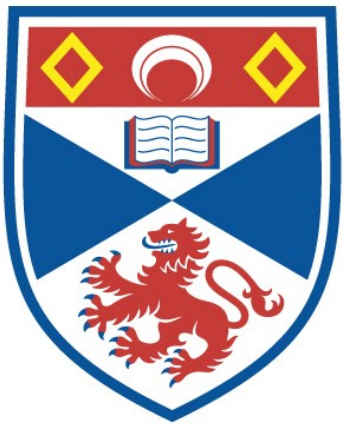
A STUDY OF RESPIRATORY RESPONSES TO VARIOUS STIMULI

Abdul Wahab Datuk Kosai

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



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ABSTRACT.

In normal subjects, the ventilatory and mouth occlusion pressure (both total mouth occlusion at 0.1 sec. from beginning of inspiration ($P_{0.1}$) and the maximum rate of change of mouth occlusion pressure, $(dp/dt)_{max.}$,) responses to CO_2 was studied. All three responses gave similar results. However, the $P_{0.1}$ response has the disadvantage that subjects anticipated and were conscious of the occlusion; thus it was not used further. In hypoxia tests too, $(dp/dt)_{max.}$ and ventilatory responses gave similar results. With added airways obstruction, the ventilatory response to CO_2 was significantly reduced whereas the $(dp/dt)_{max.}$ response was unaffected, suggesting that $(dp/dt)_{max.}$ reflects the respiratory centre output.

In patients with chronic airways obstruction, the normocapnic group showed a significantly lower ventilatory response to CO_2 but the $(dp/dt)_{max.}$ response was in the range of the normal subjects in 87% of the patients. The hypercapnic patients showed significantly lower ventilatory and $(dp/dt)_{max.}$ responses to CO_2 when compared to that of the normal subjects. The resting $PaCO_2$ showed a better correlation with $(dp/dt)_{max.}$ response than with ventilatory response. The ventilatory response in the patients showed a significant correlation with the degree of airways obstruction whilst $(dp/dt)_{max.}$ response did not show any such relationship. This suggests that $(dp/dt)_{max.}$ may be a reliable index of respiratory centre output independent of airways obstruction.

ABSTRACT (contd.)

In anaesthetized rabbits, ventilation, $(dp/dt)_{max.}$ and the average rate and total diaphragmatic electrical activity (integrated EMG) in response to CO_2 was compared. In unobstructed breathing, all four responses gave similar results. With added airways obstruction, the ventilatory response was significantly reduced whilst the other three responses were unaffected. Changes in $(dp/dt)_{max.}$ paralled changes in EMG activity with increases in PCO_2. Thus it is shown again that $(dp/dt)_{max.}$ is independent of airways obstruction and can be said to reflect the respiratory centre neural output.

In 47 normal subjects, the ventilatory response to exercise (when exercise is expressed as CO_2 produced and O_2 uptake) was studied in trained and untrained subjects. The exercise ventilatory response was compared to the CO_2 response as measured by ventilation and in some subjects by $(dp/dt)_{max.}$ response. It is found that trained subjects had a significantly lower CO_2 response and a lower ventilatory response to exercise than the untrained. The ventilatory and $(dp/dt)_{max.}$ responses correlated significantly with exercise ventilatory response. A similar correlation was found between $(dp/dt)_{max.}$ and ventilatory response to hypoxia and exercise ventilatory response.

The breathing pattern of man was also studied to find its relationship with the above findings.

This thesis is dedicated to my beloved parents and wife.

A STUDY OF RESPIRATORY RESPONSES TO VARIOUS STIMULI.

A thesis submitted to the University of St. Andrews for the degree of Doctor of Philosophy

by

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CERTIFICATE

I hereby certify that A. Wahab Kosai has spent eleven terms engaged in research work under my direction, and that he has fulfilled the conditions of General Ordinance No. 12 (Resolution of the University Court No. 1, 1967), and that he is qualified to submit the accompanying thesis for the Degree of Doctor of Philosophy.

DECLARATION

I hereby declare that the research reported in this thesis was carried out by me and that the thesis is my own composition. No part of this work has been previously submitted for a higher degree.

The research was conducted in the Department of Physiology, United College of St. Salvator and St. Leonard, University of St. Andrews, under the direction of Dr.C.G. Ingram.

ACADEMIC RECORD.

I matriculated as a research student in the Department of Physiology, University of St. Andrews in October 1973.

ACKNOWLEDGEMENTS.

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Finally, I am ever grateful to my wife, Rosna, who encouraged and helped me with everything.

CONTENTS.

INTRODUCTION

Measurements of response to hypercapnia and hypoxia gives information on the peripheral and central chemosensitivity of the individual. Various methods have been employed to assess this chemosensitivity in normals and in patients with airways obstruction. The most widely used index of respiratory centre output during hypercapnia is the ventilatory response. This can be done either by the steady-state (Schaefer 1958) or the rebreathing method of Read 1967 (Godfrey et al 1971 and Jennett and Short 1973). Both the methods gave comparable results in normal subjects (Read 1967). The rebreathing method though, has the practical advantage of mobility and takes less time. In disease the CO_2 response has been measured in brain damage (North and Jennett 1976) and in patients with chronic obstructive airways disease (Park 1965, Godfrey et al 1971, and Lane and Howell 1970). In patients with chronic airways obstruction, Scott 1920 found a reduced ventilatory response to CO_2. This results in 2 postulations to explain this observation. One idea was that the airways obstruction itself was the main cause (Cherniack and Snidal 1956) and the other was that reduced CO_2 responsiveness itself was the main factor (Park 1965). Thus indices of CO_2 response which were independent of airways obstruction, giving a true index of CO_2 responsiveness, have been employed. Amongst the methods used was the diaphragmatic electrical activity (Lourenco and Miranda 1968) and inspiratory work rate (Milic-Emili and

Tyler 1963). Whitlaw et al 1975 showed that the pressure developed at the mouth during total inspiratory airways occlusion, increased with an increase in PCO_2. This total mouth occlusion pressure was used as an index of response to hypercapnia. Matthews and Howell 1974 showed that when inspiration was occluded for a brief period, the maximum rate of change of mouth pressure, $(dp/dt)_{max.}$, could be used as an index of CO_2 response.

Animals have been widely used so that direct measurements of CO_2 responsiveness could be made. Thus Eldridge 1971 and Evanich et al 1976 used phrenic nerve activity and Altose et al 1975 used diaphragmatic electrical activity as the measured response.

In normal subjects there are wide variations in the ventilatory response to hypercapnia (Read 1967 and Godfrey et al 1971) and hypoxia (Rebuck et al 1973 and Hirshman et al 1975). The reduced CO_2 response could be due to genetic (Beral and Read 1971 and Saunders et al 1976) or to environmental factors (Schaefer 1965 and Song et al 1963). Leitch et al 1975 have shown that the ventilatory response to both hypercapnia and hypoxia may be due to genetic factors. In addition reports of lower CO_2 and hypoxia response have been reported in athletes (Byrne-Quinn et al 1971) and people living in hypoxic environment (Hurtado 1960).

Rebuck et al 1972 have shown that the ventilatory response to exercise was greater in normal subjects with higher CO_2 ventilatory response, suggesting that these two are related.

The pattern of breathing and its components, the inspiratory duration, expiratory duration and total breath duration too, give a picture of the timing and thus the inspiratory flow characteristics during breathing. Thus studies of breathing pattern in man under various respiratory stimuli have been performed by Clark and Euler 1972, Cunningham and Gardner 1972 and Jennett et al 1974.

In this study (Section 1A), the ventilatory and $(dp/dt)_{max.}$ response to CO_2 were studied in normal subjects and in chronic bronchitic patients (both normocapnic and hypercapnic) to assess their usefulness as an index of respiratory centre output. The total mouth occlusion pressure response to CO_2 and $(dp/dt)_{max.}$ response to hypoxia was also tested in normal subjects.

In Section 1B, the maximum rate of change of mouth occlusion pressure, ventilatory and diaphragmatic electrical activity response to CO_2 were studied in anaesthetised rabbits, with and without added airways resistance.

Section 2 investigates the relationship between both ventilatory and $(dp/dt)_{max.}$ response to CO_2 and the ventilatory response to exercise in a large sample of trained and untrained normal subjects.

The breathing pattern of normal subjects when subjected to hypercapnia, hypoxia and exercise was studied in Section 3 to see if there was any difference in the pattern under different respiratory stimuli.

SECTION 1A

VENTILATORY AND MOUTH OCCLUSION PRESSURE RESPONSES IN NORMAL SUBJECTS AND IN PATIENTS WITH AIRWAYS OBSTRUCTION.

INTRODUCTION

Measurements of responsiveness to hypercapnia and hypoxia are important in the determination of the sensitivity of the respiratory centre to different stimuli. By these means the respiratory drive can be determined in different individuals.

Since there is no mechanical or respiratory centre impairment in normal subjects, measurements of the ventilatory response to CO_2 and hypoxia presents no real practical problems. However, Scott 1920 demonstrated that patients with airways obstruction have a reduced ventilatory response to CO_2, and there are two possible explanations for observation. One suggests that the airways obstruction itself is the main cause for this reduction in ventilatory response, whilst the other suggests that reduced CO_2 sensitivity is the main factor. Therefore different techniques, which were independent of airways obstruction, have been employed to measure the CO_2 response.

Whitlaw et al., 1975 reported that when inspiration was made against an occluded airway, the mouth pressure, measured 0.1 second ($P_{0.1}$) after the start of inspiration, was a reliable index of response to hypercapnia. Matthews and Howell 1975 developed a similar method, which showed that the maximum rate of change of pressure at the mouth when the initial part of inspiration was totally occluded, $(dp/dt)_{max.}$, was a reliable index of CO_2

responsiveness which was independent of airways obstruction. This study was done to confirm the results obtained in normals by Matthews and Howell 1975. Whilst work on $(dp/dt)_{max.}$ measurements were made on chronic bronchitic patients, similar work was published by Matthews and Howell 1976.

In this study, the ventilatory response to CO_2 was studied in normal subjects, with and without added airways resistance, and in patients with chronic obstructive airways disease, some of whom were normocapnic and some hypercapnic. In addition $(dp/dt)_{max.}$ was used to measure the CO_2 response in these normal subjects and in patients, to see if it was a reliable index of CO_2 responsiveness independent of airways obstruction.

In normal subjects, $(P_{0.1})$ response to CO_2 was also studied. The ventilatory and $(dp/dt)_{max.}$ response to isocapnic hypoxia was studied in normal subjects to determine the reliability of $(dp/dt)_{max.}$ response as an index of respiratory centre output.

The first part of this section deals with method and results obtained for the normal subjects and the second part, for the patients. The overall discussion is dealt with in the last part of the section.

Subjects and test procedure.

25 normal, healthy male subjects (age from 18 to 27 years weight 53 to 70 kg.) underwent a CO_2 rebreathing test during which ventilation and $(dp/dt)_{max.}$ responses were simultaneously recorded. Of these subjects, 15 also underwent CO_2 rebreathing with added airways resistance. The tests were carried out at the latter part of the morning. 20 normal subjects(6 from the previous group above) underwent CO_2 rebreathing test where ventilation and $(P_{0.1})$ responses were simultaneously recorded.

To test the response to hypoxia, 20 normal subjects (all having undergone the CO_2 rebreathing test previously) were tested. During this test, simultaneous measurements of ventilation and $(dp/dt)_{max.}$ were made.

METHODS.

The CO_2 rebreathing.

a) $(dp/dt)_{max.}$ and ventilatory responses.

The CO_2 rebreathing method used in this study is similar to Reads 1967. A collapsible rubber bag of 6.0 litres capacity was placed in an air-tight box. There were two outlets, one for the rebreathing circuit and the other to which was attached a pneumotachograph. The pneumotachograph measured the flow to and from the box when rebreathing occured and these flow rates were converted into volume measurements by integration of the signals by an electrospirometer (MERCURY) (Fig. 1A-a(i)).

A linear calibration curve was obtained for volume measurements made on the electrospirometer, by pumping in and out, 1 litre of air using a one litre syringe.

There is a dead space of 200 mls. between the air sampling outlet and the mouthpiece.

Continous readings of CO_2 were done by sucking gas samples into an infra-red CO_2 analyser (BECKMAN Model LB1) and then back again into the bag. Calibration of the analyser (accuracy $\pm$ 0.1% in range of 0 to 10% CO_2) , was carried out every morning on the day of testing, using known mixtures of CO_2 in air which were initially analysed by a modified Haldane-Lloyd apparatus. The CO_2 analyser was switched on overnight prior to a test for greater stability.

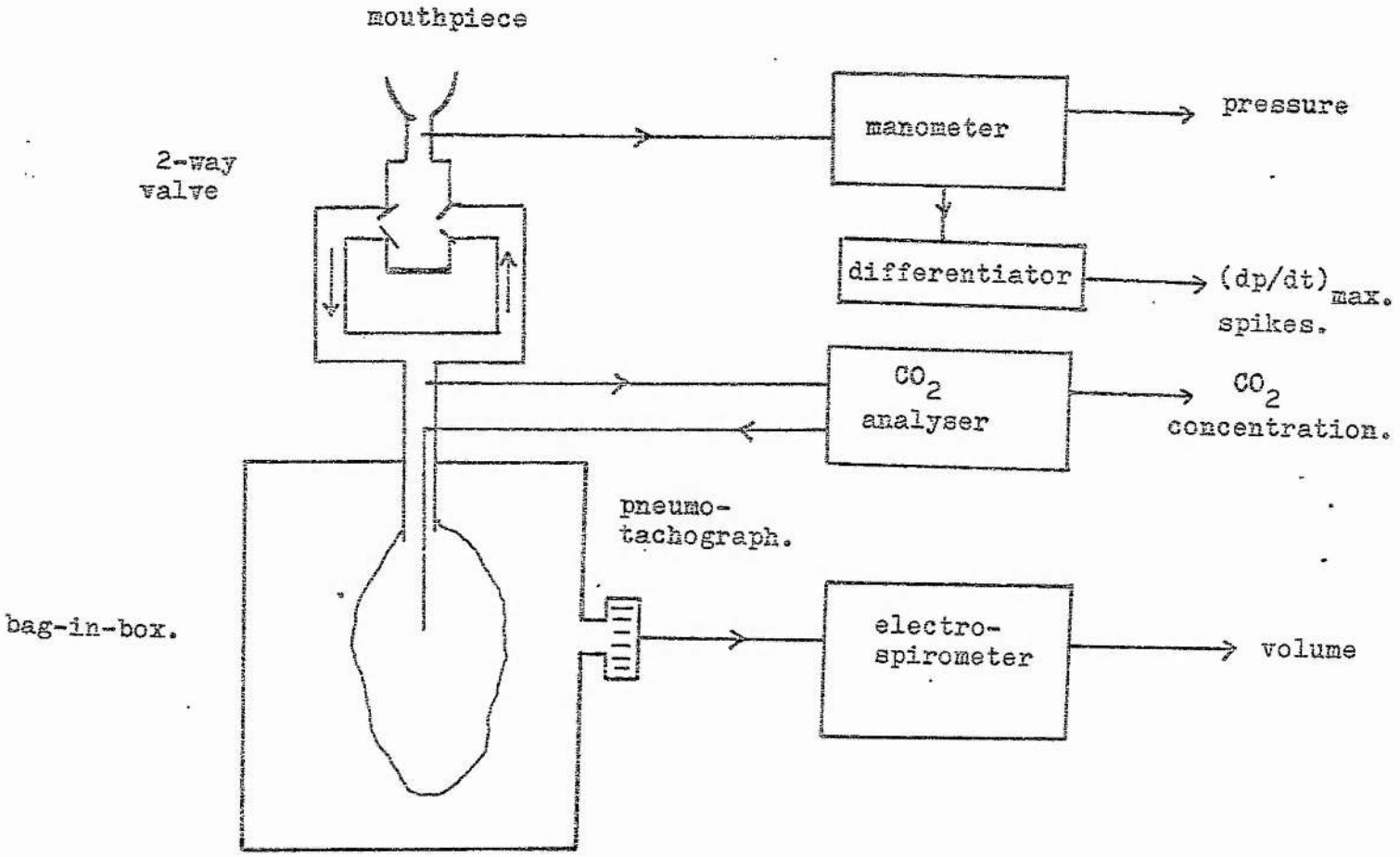


Fig. IA- a(i) Diagram of apparatus used to record ventilatory and $(dp/dt)_{max.}$ responses to CO_2.

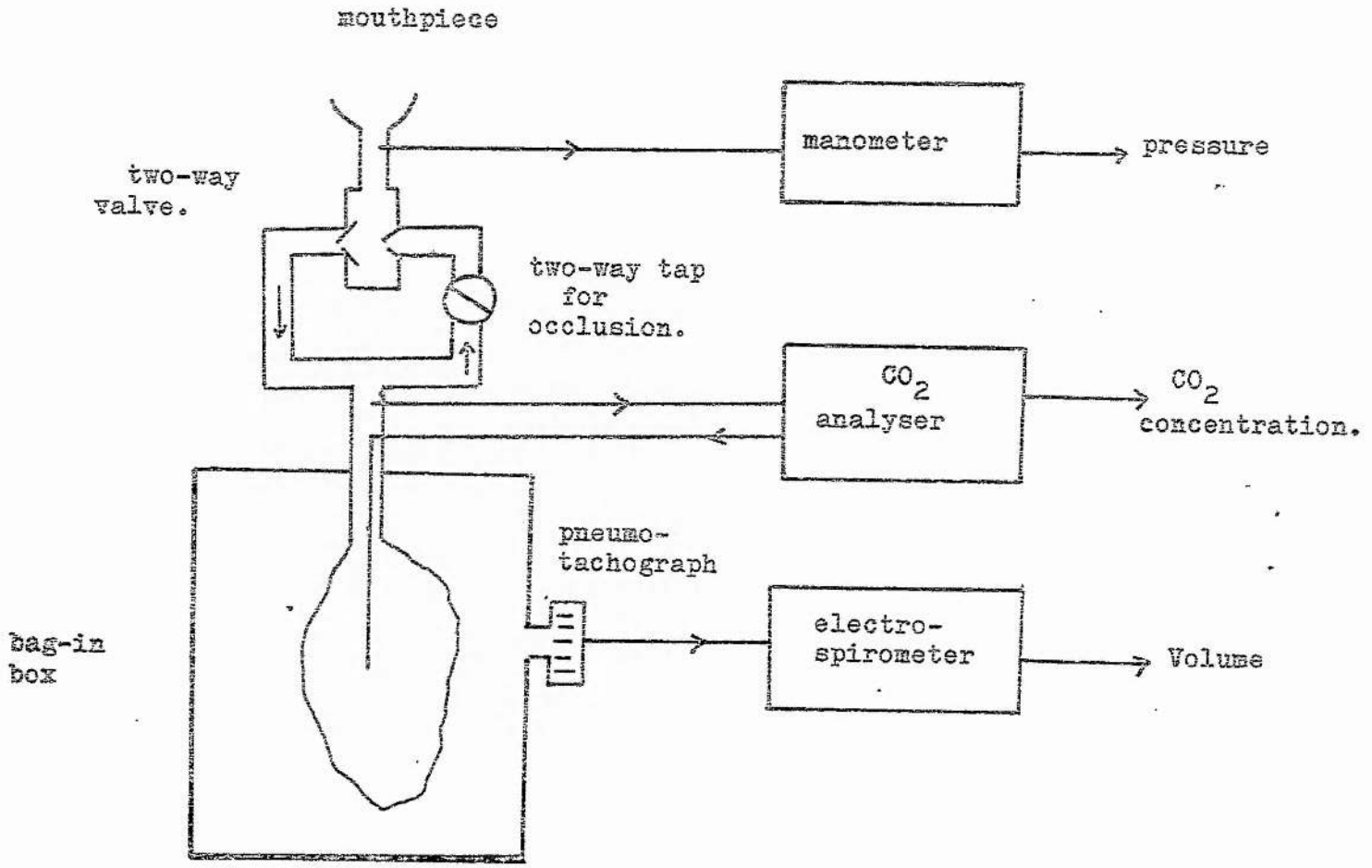


Fig. IA-a (ii) Diagram of apparatus used to record ventilatory and $P_{0.1}$ responses to CO_2

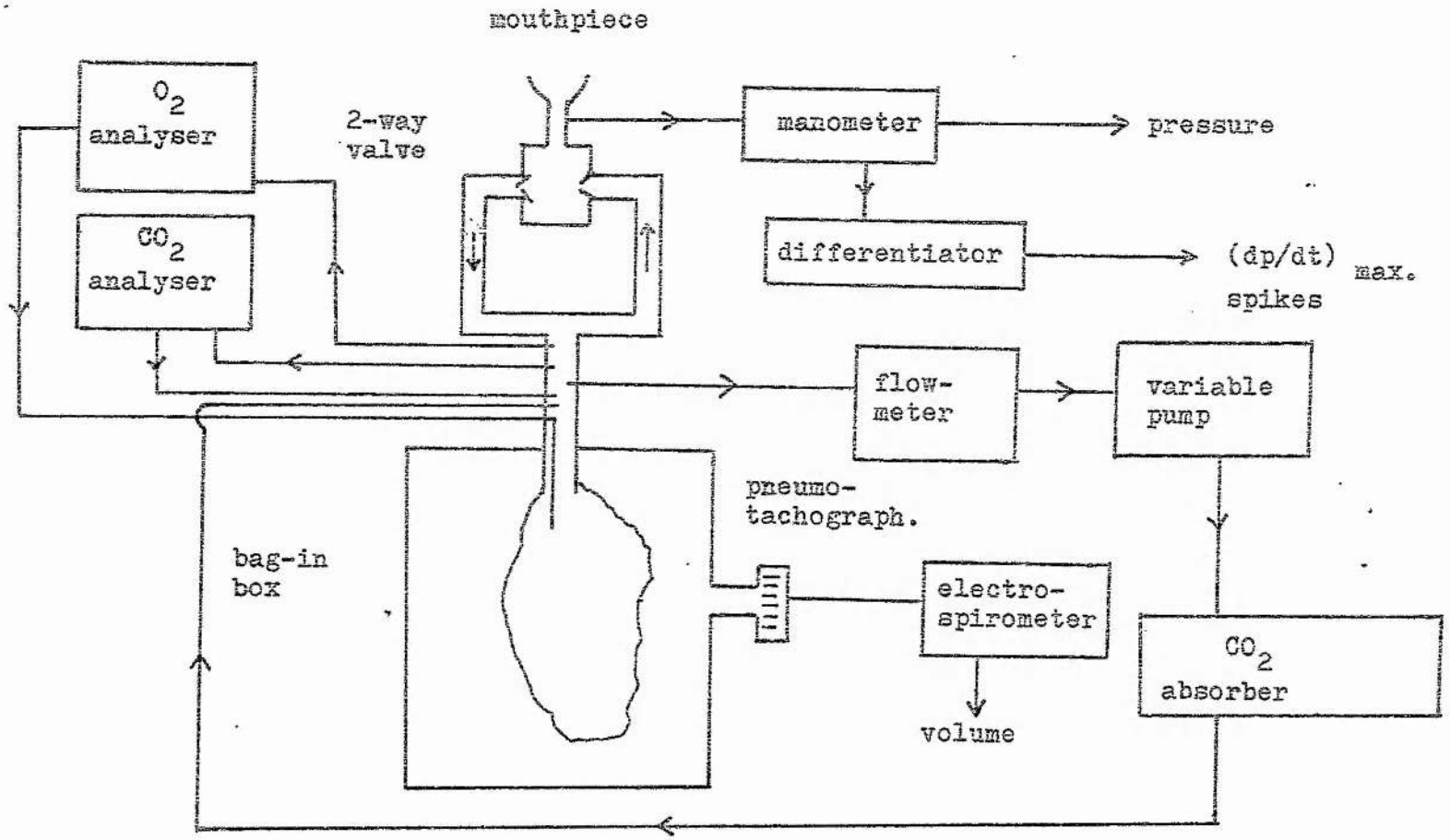


Fig. IA- a (iii) Diagram of apparatus used to record ventilatory and $(dp/dt)_{max.}$ responses to isocapnic hypoxia.

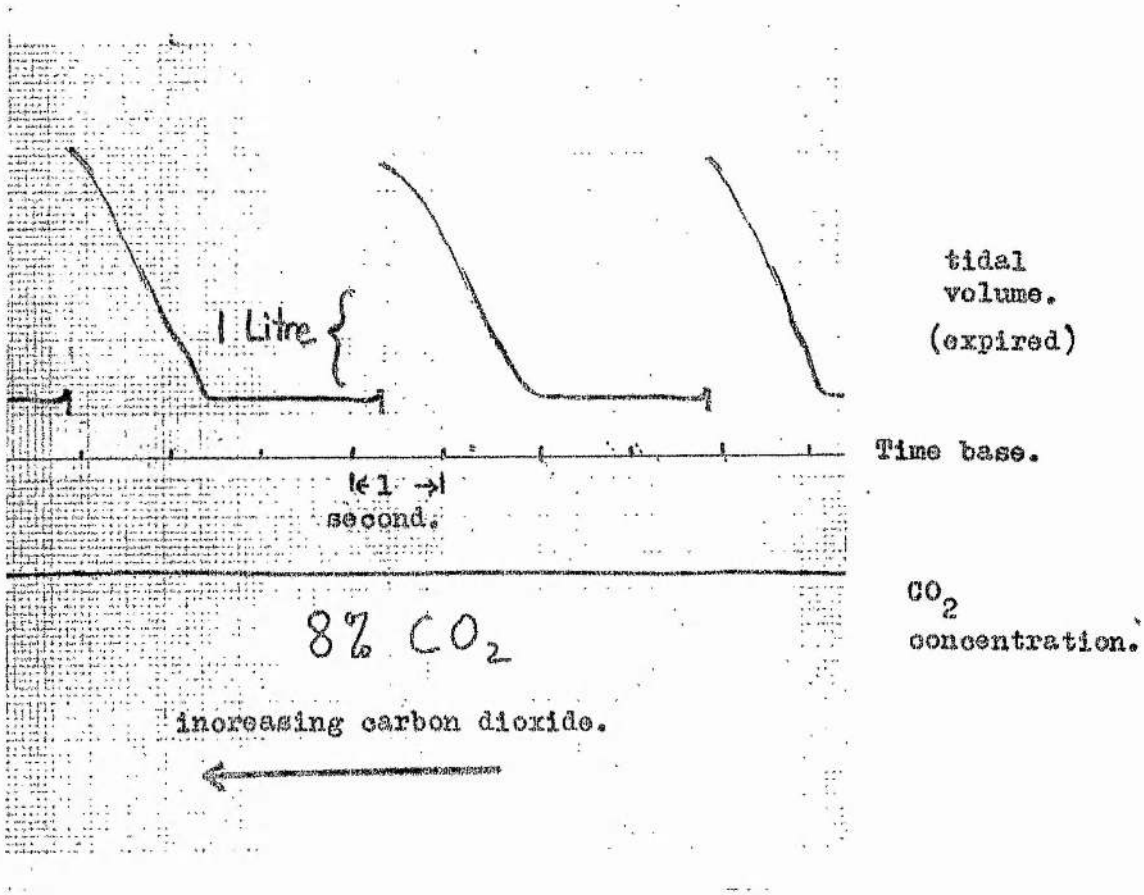


Fig. 1A-1a. Typical trace of simulataneous recordings made during CO_2 rebreathing test.

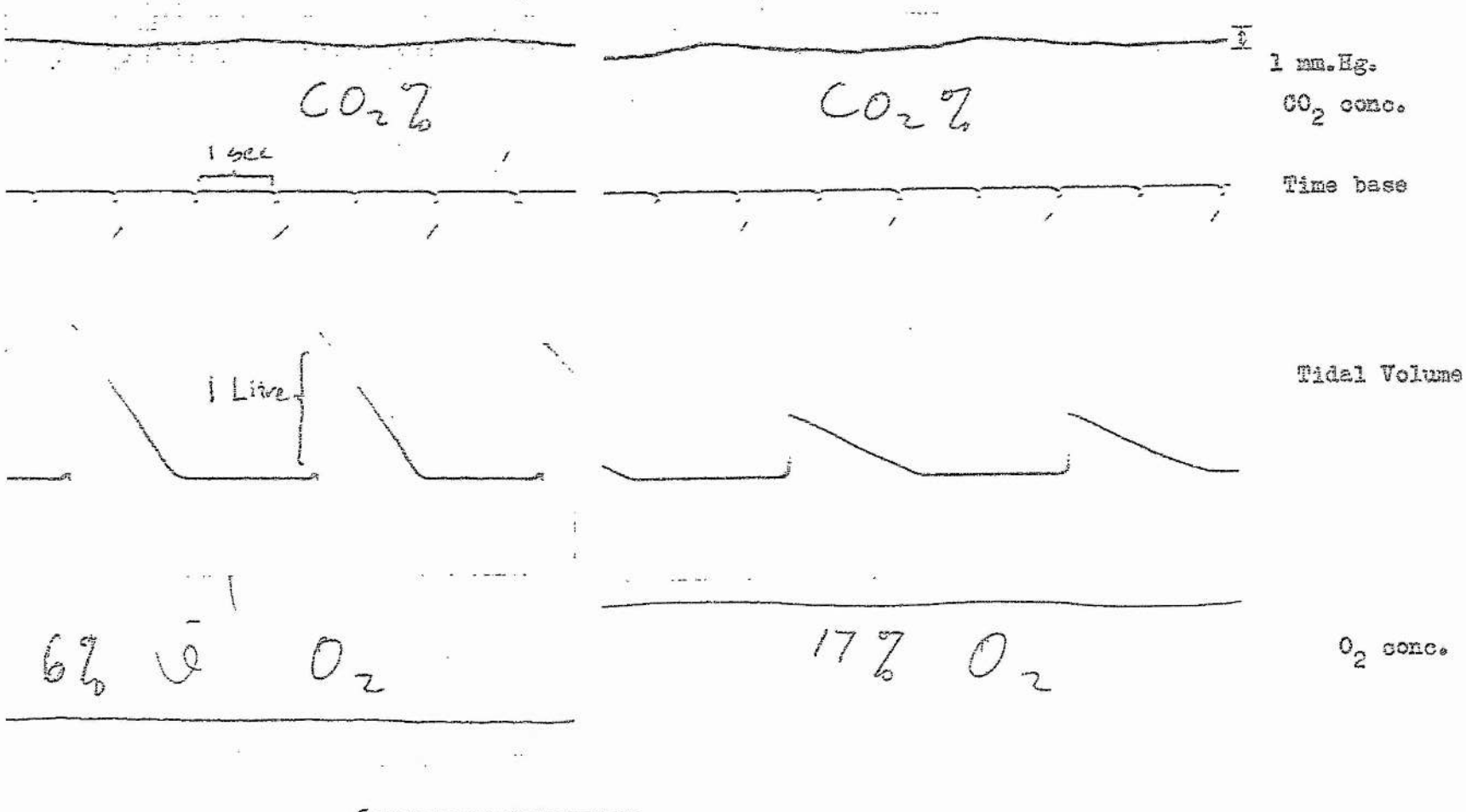
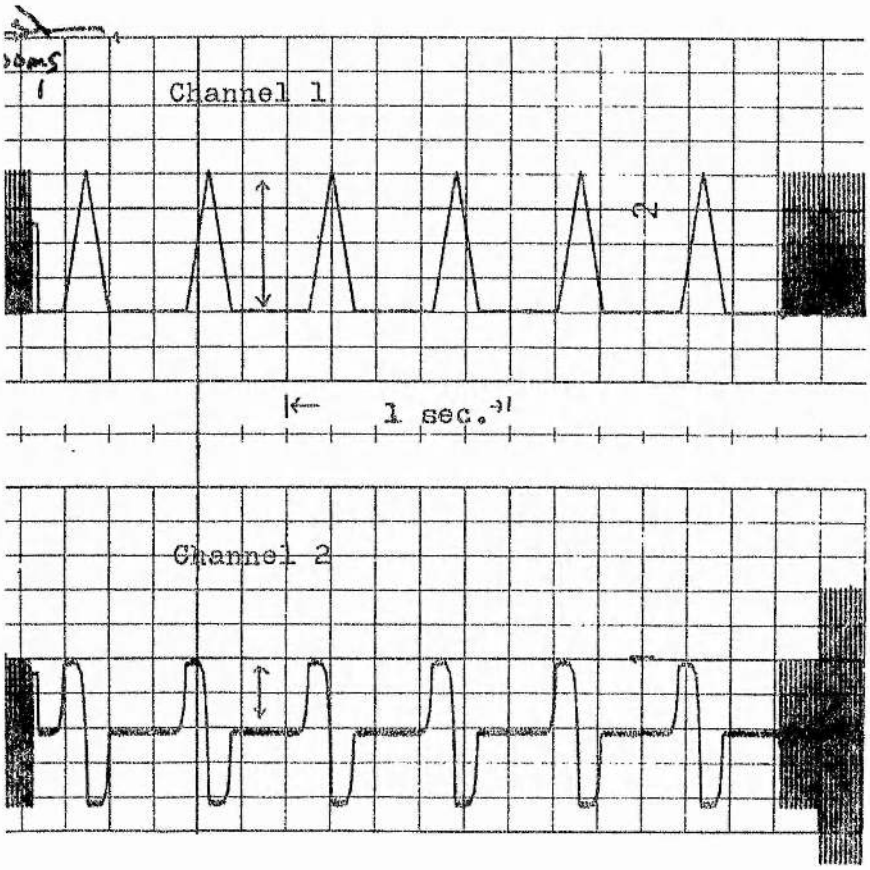


Fig. 1A-1b. Typical trace of simultaneous recordings made during progressive hypoxia test. (isocapnic)
Right.- recording during early part of test. Left- at last part of test.



input 1 volt. (arrows pointing)

corresponding differentiated signal (arrows pointing)

Fig. 1A-h (i)

Calibration of $(dp/dt)_{max.}$ spikes.

Channel 1 gives an input signal of known voltage ramp pulse (which corresponds to pressure change signals). Channel 2 records the differentiated corresponding signal from Channel 1 as spikes, the height of which gives $(dp/dt)_{max.}$ measurements.

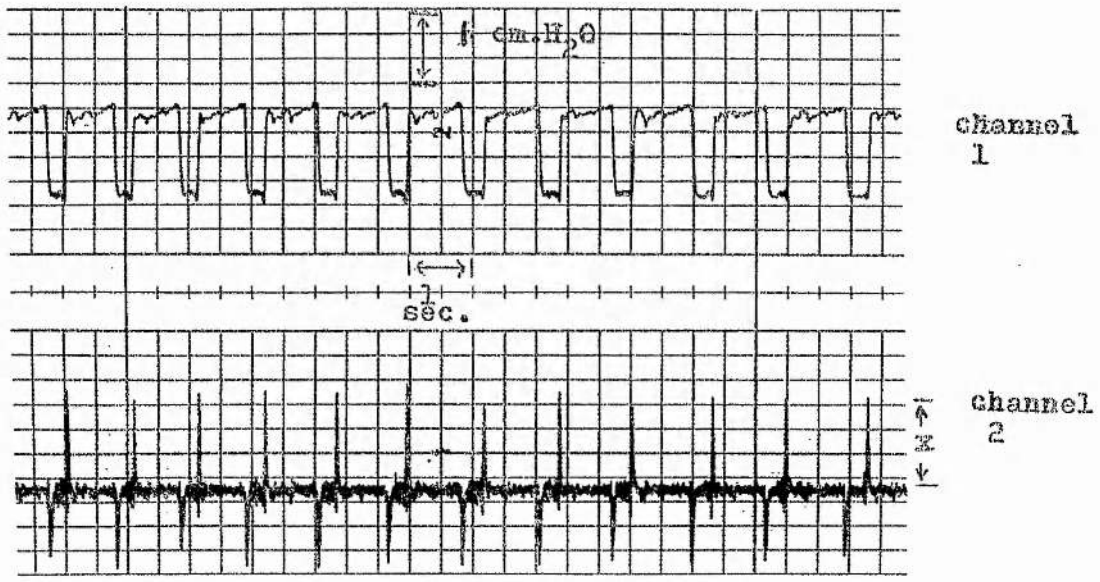
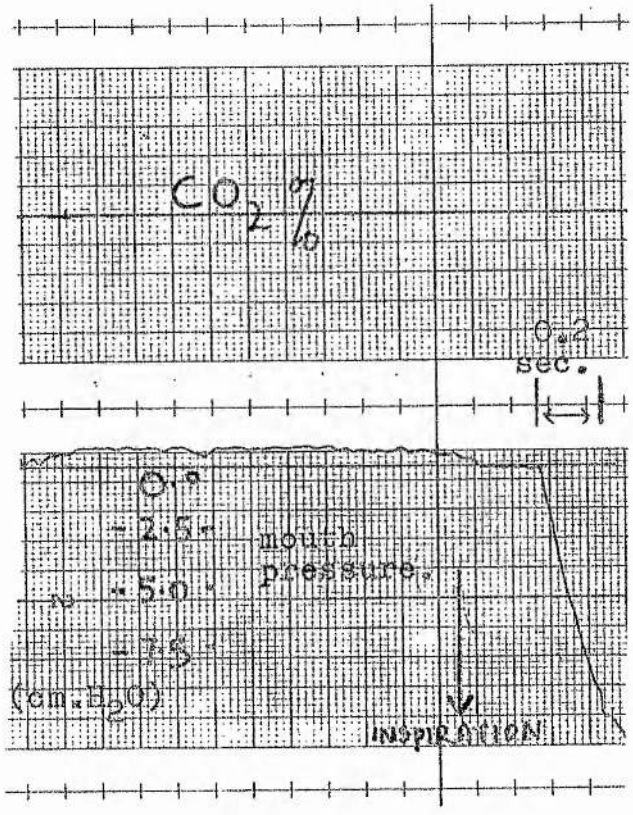


Fig. 1A-h (ii)

Tracing of maximum rate of change of pressure during transient inspiratory occlusion, $(dp/dt)_{max.}$, recorded as spikes(channel 2) with the corresponding mouth pressure (channel 1).

height of x represents $(dp/dt)_{max.}$ measurement.



CO_2 Concentration.

time base.

mouth pressure at occlusion.

Fig. 1A-b(iii). Tracing of mouth occlusion pressure during CO_2 rebreathing. The zero pressure line is drawn.

A two-way Douglas valve (MORGAN) was attached at the mouth open end of the circuit. The inspiratory disc of the Douglas valve has an opening pressure of 1 cm. H_2O which produced a transient inspiratory occlusion. A tube was attached to the outlet between the mouthpiece and the disc in the valve for recording mouth pressure changes. This tube was attached to a pressure transducer (Hilger Micromanometer MDC 41a), from which pressure change signals were fed into a fast responding two-channel pen recorder (Gould Brush). In one channel mouth pressure changes were recorded whilst in the other, an electronic circuit differentiated the pressure signals to produce spikes, the height of which gave the $(dp/dt)_{max.}$ measurement. Simultaneous recordings of ventilation and CO_2 concentration were recorded on a two-channel pen recorder.

Treatment of results.

As stated above the height of a spike is proportional to $(dp/dt)_{max.}$. The whole test duration was divided into 30 second components and all the spikes were added for this 30 second period and then divided by the spike frequency to give the mean $(dp/dt)_{max.}$ for that particular 30 second period.(Fig. 1A-b(ii)).

Tidal volume measurements were added for each 30 second period and then multiplied by two to give minute ventilation. The PCO_2 for each 30 second period was taken at the last quarter of each period.(Fig. 1A-1a)

Added resistance breathing.

A rubber bung with a small opening which gave a flow

resistance of + 4.5 cm.H_2O $sec.^{-1}L^{-1}$ was introduced between the mouth and the respiratory valve in the circuit.

Calibration of $(dp/dt)_{max.}$ response

Between the valves and mouthpiece, an opening for an outlet tubing was placed, leading to a pressure manometer. The manometer was first calibrated to find the voltage given out when there is a maximum deflection. Using a pressure calibrator, it was found that, a deflection of 32 mm.H_2O gives 1 volt output. Using a voltage calibrator, a volt per second was passed into the pressure tracing on a Gould Brush fast responding recorder. (see Fig.1A-b(i)). The signal is then differentiated to give spikes, height of which represents the voltage input per second. Hence when actual pressure changes were recorded, the resultant voltages were differentiated. The apparatus was found to be very stable.

b) $(P_{0.1})$ and ventilatory responses.

The rebreathing circuit used was similar to the one used for $(dp/dt)_{max.}$ response to CO_2. A two-way tap was inserted in the inspiratory line. The same equipment for analysing CO_2 and ventilation was used.(Fig.1A-a(ii))

During rebreathing, random total occlusion within each 30 second period was made during expiration, which allowed the expired air to pass into the bag, but meant that the subsequent inspiration would be made against an occluded airway. The occlusion lasted for the complete inspiration. The resulting mouth pressure generated

against the occluded inspiratory airways was measured using a pressure transducer (Hilger Micromanometer).

Recordings of ventilation (from individual tidal volume) and CO_2 concentrations were made on a two-channel recorder (Devices). The total occlusion mouth pressure recordings was made on a fast responding recorder.

The total occlusion pressure readings were made at 100ms. from the start of inspiration ($P_{0.1}$). As a precaution against irregular breathing after each occlusion, all the subjects were told in advance to continue to breathe normally after occlusion.

Treatment of ($P_{0.1}$) measurements.

A typical tracing of ($P_{0.1}$) measurement is shown in Fig. 1A-**b**(iii). With inspiratory occlusion, mouth pressure drops and this is recorded on the fast responding pen-recorder which was kept running at a speed of 5 mm per second. The pressure at 0.1 second was taken as the ($P_{0.1}$), and the corresponding PCO_2 at this time was measured. The total duration of rebreathing was divided into 30 second periods and occlusion was done randomly within this 30 second period to prevent anticipation by the subject.

Calibration of ($P_{0.1}$).

A sensitive pressure manometer (Hilger Micromanometer) was used to record mouth occlusion pressure. A pressure calibrator (London Casella) was used to calibrate the micromanometer. A known pressure was introduced into the

micromanometer which in turn gave a deflection on the pen-recorder. Thus different heights on the recorder chart correspond to known pressure.

c) Rebreathing techniques (similar to Read's 1967)

The initial bag CO_2 concentration was 7% CO_2 in O_2 for normal subjects. In patients, different initial concentrations were put into the bag, depending on the patients resting $PaCO_2$. Thus the normocapnic patients had an initial bag PCO_2 similar to that for normal subjects, whilst in the hypercapnic patients, the initial bag PCO_2 was slightly higher. This ensured rapid equilibrium on rebreathing, between PCO_2 in bag, lungs and pulmonary capillary blood. (Campbell and Howell 1962)

All the subjects underwent the same rebreathing procedure. The subjects were seated comfortably and breathed room air for 1 minute to get used to the experimental equipment. Rebreathing lasted for 4 to 5 minutes or less if they could not carry on.

The CO_2 ventilatory response curve can be expressed in terms of its slope or "S" (litres $min^{-1}mm.Hg^{-1}$) and the intercept of the x axis as B (in mm.Hg.) as shown by Lloyd et al., 1958.

The slopes in normal subjects were mainly obtained for data between about 43 and 70 mm.Hg PCO_2.

Blood gas determinations

The resting arterial PCO_2 in patients was determined by direct measurements from blood samples. $PaCO_2$ was also checked by using an indirect method. The subjects rebreathed from a small bag (2 litre) of 100% oxygen for

1.5 mins., rested for two minutes, then rebreathed again for 20 seconds. The concentration of CO_2 in the bag was determined by a CO_2 analyser and after corrections made for arterial-venous difference, the $PaCO_2$ was determined. In all cases where these checks were carried out, there was no significant difference in the resting $PaCO_2$ measured by direct blood determination or by the indirect method.

Calibration of CO_2 analyser.

For the normal subjects and normocapnic patients, the CO_2 analyser was calibrated for 1% to 10% CO_2. For the hypercapnic patients the gain on the CO_2 analyser was reduced so that a maximum reading of 12% CO_2 can be obtained by extrapolation on the CO_2 calibration curve.

Method used in Isocapnic Hypoxia Test. (progressive)

The method used in this experiment is similar to the one used by Rebuck et al., 1973.

In this experiment a rebreathing circuit was used (Fig. 1A-a (iii)) A six-litre rebreathing bag in a sealed box was filled with 7% CO_2, 20 to 22% O_2, and the rest nitrogen. End-tidal measurements of O_2 and CO_2 were continuously made from samples taken near the mouth and after passing through the CO_2 and O_2 meters were returned to the bag. The gas analysers used were an infra-red CO_2 analyser accurate to $\pm$ 0.1% over range 0 - 10%, and a paramagnetic O_2 analyser (Servomex) with a 90% response time of 0.15 sec, and $\pm$ 0.1% accuracy.

Ventilation was measured using a pneumatograph attached to the outlet in the box and connected to a electro-spirometer. A two-way low-resistance Douglas

valve was attached to the mouth-piece (as used in the CO_2 rebreathing experiment). The opening pressure of the valve, at 1 cm.H_2O, provided an imperceptible transient occlusion of inspiration. An outlet from the mouth-piece connected to the manometer measured the pressure between the mouth and the valve and this was recorded in a fast-responding 2-channel recorder. The pressure change was recorded in one channel and in the other channel, the pressure wave signal was electronically differentiated and recorded as spikes.

The resistance of the circuit was 0.6 cm.H_2O/litre per sec.

Before starting the experiment, the subject was made to sit comfortably for 10 minutes after which he breathed room air through the mouth piece for a further 5 minutes. After this period, at the end of a normal expiration, the tap was turned to connect the subject to the rebreathing bag. The subject was asked to take 2 to 3 deep breaths to facilitate mixing between lung and bag. When the end-tidal PCO_2 plateau is reached, usually between 15 to 20 seconds a pump connecting the bag to a soda lime cannister by-pass was switched on. A variable flowmeter was used to control the flow through the CO_2 scrubber so that the end-tidal PCO_2 was kept constant to within $\pm$ 1 mm.Hg. of the initial mixed-venous level throughout the experiment. The initial PO_2 ranged from 140 to 160 mm.Hg. and was allowed to decrease to a minimum of 30 to 40 mm.Hg.

PCO_2, PO_2 and ventilation were continuously recorded on a Devices four channel recorder.

Repeat testing

Repeat tests were made for the both types of hypercapnic response tests (also with added resistance) and the hypoxic response test. To prevent bias in the treatment of results, the results from the first test only were used for statistical analysis.

Treatment of data from hypoxia test. (Fig.1A-1b)

The ventilatory and $(dp/dt)_{max.}$ responses to hypoxia and the corresponding bag PO_2 was calculated for every 30 seconds throughout rebreathing, until the last 30 seconds where it was calculated for 15 seconds. The mean ventilation (from individual tidal volumes) and the mean $(dp/dt)_{max.}$ (from individual spikes) was calculated. The resulting relationship obtained, when ventilation was plotted against P_AO_2 was hyperbolic. This hyperbolic relationship was converted to a linear function as suggested by Weil et al., 1970, by an equation similar to one originally suggested by Lloyd et al., 1958. This equation relates ventilation and alveolar PO_2 as follows, $\dot{V}_E = \dot{V}_EO+A/(PAO_2-32)$, where $\dot{V}_E$ is minute ventilation in litres per minute; PAO_2 is the alveolar O_2 tension in mm.Hg and $\dot{V}_EO$ (or $\dot{V}O$) is the asymptote for ventilation obtained by extrapolation. Parameter A describes the shape of the curve in that the bigger the value of A, the greater is the hypoxic ventilatory drive. The constant 32 represents the PAO_2 at which the ventilation - PAO_2 curve approaches infinity. Byrne-Quinn et al., 1971, Weil et al., 1972, Rebuck et al., 1973 and Kelsen et al.,

1976 amongst others found that a simple linear function was obtained by plotting $\dot{V}_E$ against $1/(PAO_2 - 32)$. The slope of the response line calculated using the least-squares regression method is A and its y intercept is $\dot{V}_E O$ (Weil et al., 1972) or $\dot{V}O$.

Similar slopes were constructed for $(dp/dt)_{max.}$ response hypoxia by plotting the respective $(dp/dt)_{max.}$ values against PAO_2 and against $1/(PAO_2 - 32)$. The slope obtained for this in the present study is called "A $(dp/dt)_{max.}$".

RESULTS

Normal subjects

Ventilatory response to CO_2 (Table 1A-1).

In the 25 normals studied, the ventilatory response to CO_2 ranges from 1.14 to 4.04 L min^{-1} $mmHg^{-1}$. (mean 2.55)

The B intercept on the x axis of the ventilatory response to CO_2 slope ranges from 33.5 to 46.3 mmHg. (mean 39.5)

$(dp/dt)_{max.}$ response to CO_2. (Table 1A-1).

When the CO_2 response is measured in terms of $(dp/dt)_{max.}$, it ranges from 1.02 to 3.50 cm.H_2O sec^{-1} $mmHg^{-1}$. (mean 2.38)

The B intercept on the x axis of $(dp/dt)_{max.}$ response to CO_2 slope ranges from 31.9 to 46.6 mmHg. (mean 39.9)

Correlation between ventilatory and $(dp/dt)_{max.}$ response to CO_2.

There was a significant correlation between ventilatory and $(dp/dt)_{max.}$ response to CO_2 in the group of 25 normal subjects tested.
($r = 0.814$ $p = <0.001$) See Fig. 1A-5.

Subjects.	$\Delta \dot{V}_E / \Delta PCO_2$	B	$\frac{\Delta (dp/dt)_{max.}}{\Delta PCO_2}$	B_I
I-I	2.59	43.7	3.50	46.6
I-2	I.30	37.8	I.50	38.7
I-3	2.87	43.7	3.32	46.0
I-4	3.I3	4I.5	3.24	42.9
I-5	I.29	42.7	I.20	39.8
I-6	3.76	46.3	3.02	45.6
I-7	2.36	4I.5	I.84	4I.6
I-8	I.73	34.9	I.45	3I.9
I-9	I.43	37.5	I.63	38.I
I-I0	I.7I	42.4	I.43	39.0
I-II	I.80	36.8	I.66	36.9
I-I2	I.I4	33.5	I.34	36.9
I-I3	2.6I	38.2	2.I7	38.9
I-I4	3.67	34.6	3.73	32.I
I-I5	2.I2	4I.9	I.45	38.I
I-I6	3.0I	44.I	3.05	44.3
I-I7	3.84	38.4	2.43	38.7
I-I8	4.04	36.4	3.05	4I.2
I-I9	2.I5	36.5	I.55	39.7
I-20	3.50	40.4	3.I2	38.5
I-2I	2.66	40.I	3.40	40.3
I-22	3.80	37.3	2.85	40.2
I-23	3.70	43.2	3.63	4I.I
I-24	2.I5	37.4	2.85	39.7
I-25	I.40	38.0	I.02	42.8
Mean	2.55	39.5	2.38	39.9
SD.	0.94	3.4	0.90	3.6
SE.	0.20	0.7	0.I8	0.7

Table IA-I Results of CO_2 rebreathing test, showing ventilatory and $(dp/dt)_{max.}$ responses.

Table IA-I. Units used.

$\Delta \dot{V}_E / \Delta PCO_2$ = ventilatory response to CO_2

litres min^{-I} $mm.Hg.^{-I}$

B = x axis intercept on the CO_2 ventilatory response slope.

mm.Hg.

$\frac{\Delta (dp/dt)_{max.}}{\Delta PCO_2}$ = $(dp/dt)_{max.}$ response to CO_2

$cm.H_2O$ sec^{-I} $mm.Hg^{-I}$

B_I = x axis intercept on the $(dp/dt)_{max.}$ response to CO_2 slope.

mm.Hg.

CO_2 rebreathing in normal subjects.

In this study (Section 1A) the range of CO_2 ventilatory response lies within the reported range for normal subjects. The mean value for the group too are comparable with previously reported studies.

Investigation	Sample size	Mean SCO_2	SD
Read (1967)	21	2.65	± 1.21
Clark (1968)	19	3.29	± 1.42
Godfrey et al (1971)	7	2.05	± 0.97
Saunders et al (1972)	50	2.17	± 0.79
Rebuck et al (1972)	11	1.87	± 0.62
Jennett and Short (1973)	66	2.35	± 1.10
Zackon et al (1976)	10	3.20	± 0.30
Present study	25	2.55	± 0.94

Results obtained for ventilatory response to CO_2 in normal subjects using Read's rebreathing method.

Subject 1-1

No Resistance

PCO_2 (mm.Hg.)	$\dot{V}_E$ ($L.min^{-1}$)	$(dp/dt)_{max.}$ ($cm.H_2O\ sec^{-1}$)
48.1	18.20	14.67
51.3	20.43	17.02
53.5	24.58	23.20
55.3	27.09	27.53
57.7	32.75	33.33
59.9	38.35	38.33
61.7	43.22	49.94
63.1	49.44	56.00
65.7	52.19	64.74
67.0	65.58	76.66
68.4	70.87	81.92

Added Resistance.

44.9	10.85	11.50
51.3	15.27	16.72
54.3	20.86	26.72
58.3	24.36	35.20
60.0	30.68	45.44
62.4	32.05	51.12
66.7	37.69	69.89
69.1	41.65	83.63
71.0	47.36	94.69

Table. 1A-2 Experimental data during CO_2 rebreathing in one subject.

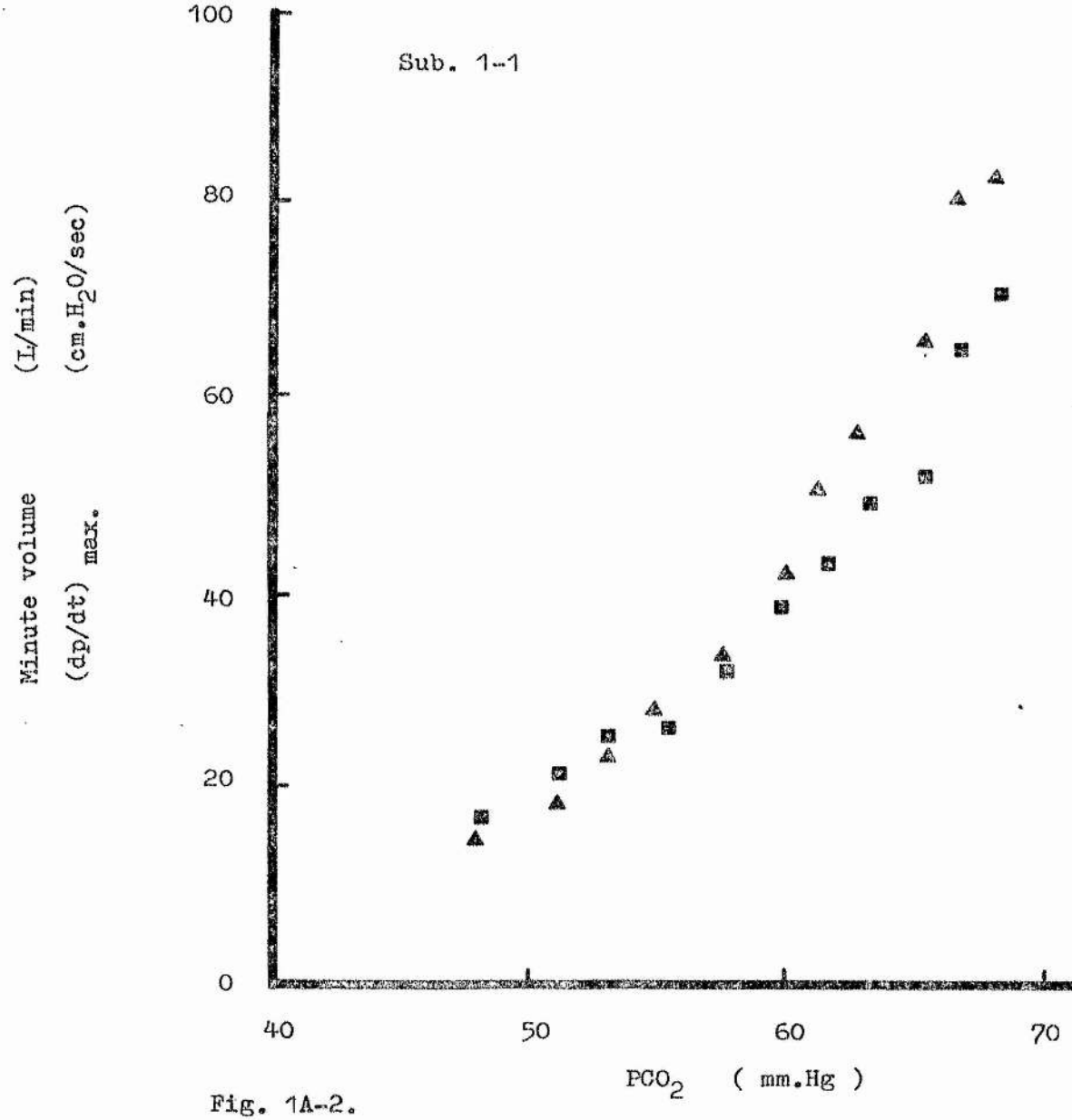


Fig. 1A-2.

Ventilatory ■ and $(dp/dt)_{max.}$ △ response to CO_2 in a representative normal subject.

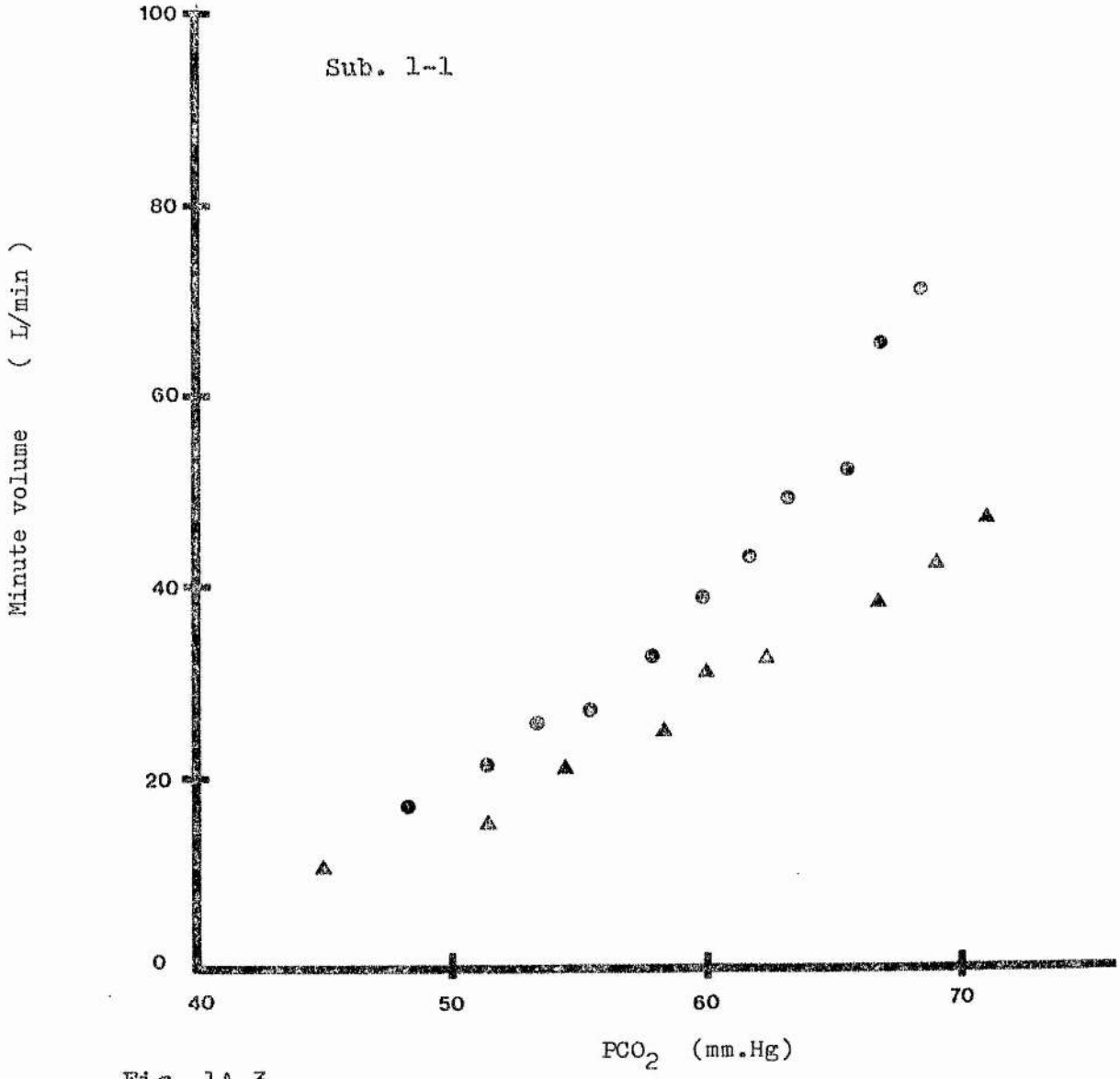


Fig. 1A-3.

Effect of an external flow resistance on the ventilatory response to carbon dioxide in a normal subject

● No resistance

▲ + 4.5 cm H_2O s^{-1} L^{-1} resistance.

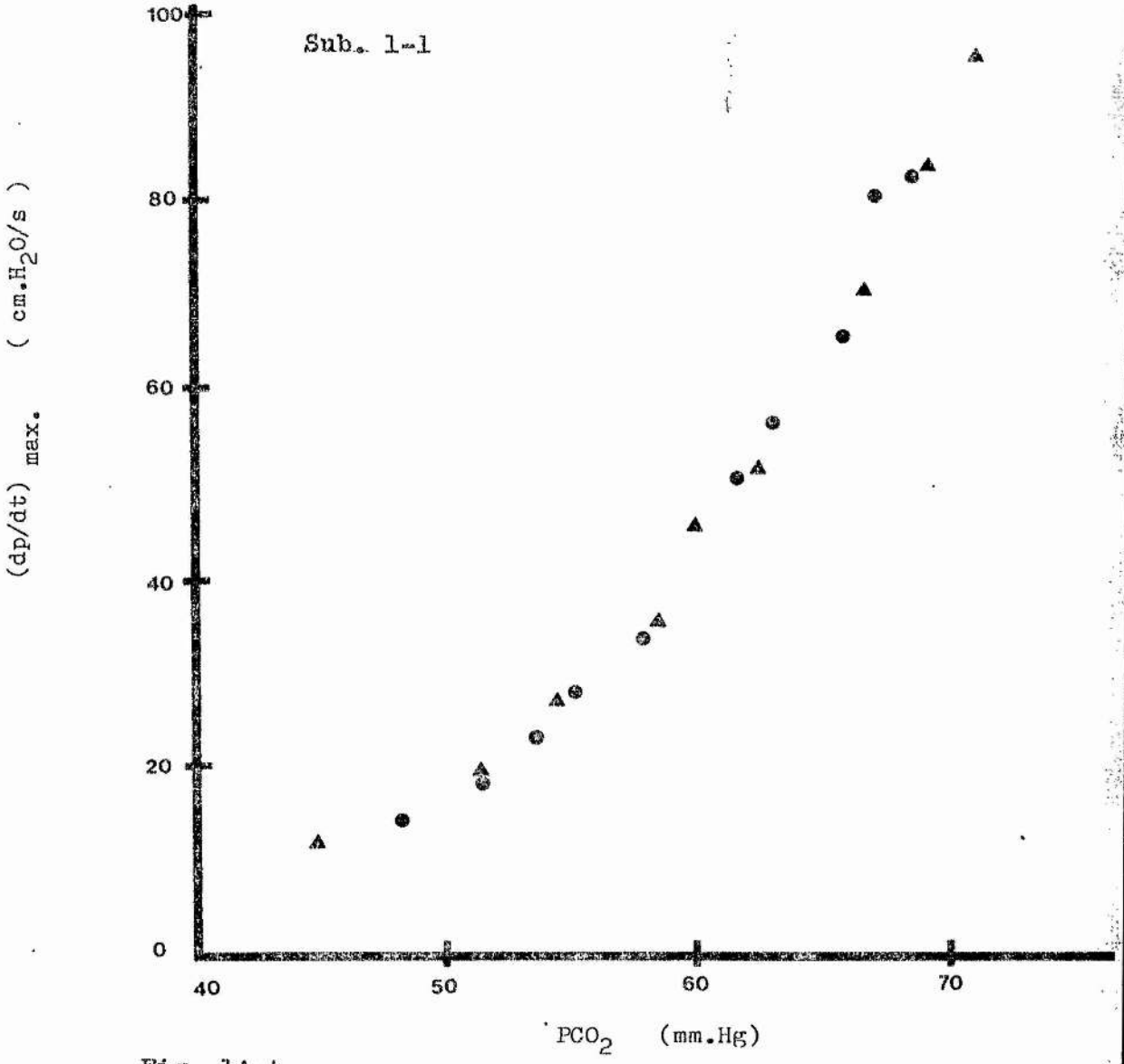


Fig. 1A-4.

Effect of an external flow resistance on the $(^{dp}/dt)_{max.}$ response to carbon dioxide in a normal subject.

● No resistance.

▲ + 4.5 cm H_2O s^{-1} L^{-1} resistance.

Subjects.	No Resistance				Added Resistance			
	$\Delta \dot{V}_E / \Delta PCO_2$	B	$\frac{\Delta (dp/dt)_{max.}}{\Delta PCO_2}$	B_1	$\Delta \dot{V}_E / \Delta PCO_2$	B	$\frac{\Delta (dp/dt)_{max.}}{\Delta PCO_2}$	B_1
I-I	2.59	43.7	3.50	46.6	I.40	39.I	3.30	45.2
I-2	I.30	37.8	I.50	38.7	0.68	27.6	I.20	37.5
I-3	2.87	43.7	3.32	46.0	I.60	39.5	3.27	46.7
I-4	3.I3	4I.5	3.24	42.9	I.44	33.7	2.85	40.2
I-5	I.29	42.7	I.20	39.8	0.73	32.8	I.I9	36.6
I-6	3.76	46.3	3.02	45.6	I.68	39.5	2.93	45.2
I-7	2.36	4I.5	I.84	4I.6	I.50	37.9	2.I5	42.6
I-8	I.73	34.9	I.45	3I.9	0.5I	9.5	I.70	37.I
I-9	I.43	37.5	I.63	38.I	I.00	29.3	I.60	38.5
I-I0	I.7I	42.4	I.43	39.0	I.I6	36.7	I.34	42.7
I-II	I.80	36.8	I.66	36.9	0.94	27.2	I.74	36.4
I-I2	I.I4	33.5	I.34	36.9	0.80	27.6	I.82	34.9
I-I3	2.6I	38.2	2.I7	38.9	I.82	39.8	2.37	4I.8
I-I4	3.67	34.6	3.73	32.I	I.94	32.6	3.6I	32.2
I-I5	2.I2	4I.9	I.45	38.I	0.79	26.2	I.9I	39.8
Mean	2.23	38.0	2.I5	39.6	I.I9	3I.9	2.I9	39.8
SD	0.85	7.5	0.9I	4.4	0.45	7.9	0.80	4.I
SE	0.22	I.9	0.24	I.4	0.I2	2.0	0.2I	I.0

Table IA-3a. Results of CO_2 rebreathing, showing ventilatory and $(dp/dt)_{max.}$ responses with and without added airways resistance.

Table IA-3b. Repeats of ventilatory and $(dp/dt)_{max.}$ responses to CO_2.

Subjects.	No resistance		Added resistance	
	$\Delta \dot{V}_E/\Delta PCO_2$	$\frac{\Delta (dp/dt)_{max.}}{\Delta PCO_2}$	$\Delta \dot{V}_E/\Delta PCO_2$	$\frac{\Delta (dp/dt)_{max.}}{\Delta PCO_2}$
I-I	2.59 2.79	3.50 2.85	I.40 I.54	3.30 3.00
I-2	I.30 I.75 I.90	I.50 2.00 I.90	0.68 0.75	I.20 I.50
I-3	2.87 3.30	3.32 3.I0	I.60 I.85	3.27 3.25
I-4	3.I3 2.65	3.24 3.60		
I-II	I.80 I.65	I.66 I.50		
I-I4	3.67 3.I0	3.73 3.20		
I-I5	2.I2 I.95	I.45 I.90		
I-25	I.40 I.30	I.02 I.30		

Units used in Tables IA-3a and IA-3b.

$\Delta \dot{V}_E/\Delta PCO_2$ ventilatory response to CO_2. litres $min^{-I}{}_{mm.Hg}{}^{-I}$

B intercept on x axis of ventilatory CO_2 response slope. (mm.Hg)

$\frac{\Delta (dp/dt)_{max.}}{\Delta PCO_2}$ $(dp/dt)_{max.}$ response to CO_2. $cm.H_2O\ sec^{-I}{}_{mmHg}{}^{-I}$

B_1 intercept on x axis of $(dp/dt)_{max.}$ response to CO_2 slope. (mm.Hg.)

Normal subjects

Effects of resistance on ventilatory and $(dp/dt)_{max.}$ responses to CO_2. (Table 1A-3a)

15 subjects undergo both CO_2 response test first without resistance, then with added resistance of + 4.5 cm $H_2O s^{-1} L^{-1}$. Results obtained are summarised below:-

Ventilation response
(Litres/min/mmHg CO_2)

	Without resistance	With resistance	% Change
Mean	2.23	1.19	-47
SD	0.85	0.45	
SE	0.22	0.12	
Range	1.14 to 3.76	0.4 to 1.6	-70 to -29

$p = < 0.001$ Significant difference

$(dp/dt)_{max.}$ response
(cm H_2O/sec/mmHg CO_2)

	Without resistance	With resistance	% Change
Mean	2.16	2.19	+1
SD	0.91	0.80	
SE	0.24	0.21	
Range	1.20 to 3.73	1.19 to 3.61	-19 to +35

No significant difference.

B (X-axis intercept in mm.Hg.)

Ventilatory slope

	Without Resistance	With Resistance	% Change
Mean	38.0	31.9	-16
SD	7.5	7.9	
SE	1.9	2.0	
Range	33.5 to 43.7	9.5 to 39.8	-72 to + 4

$p = < 0.001$ Significant difference

$(dp/dt)_{max.}$ slope

	Without Resistance	With Resistance	% Change
Mean	39.6	39.8	< +0.1
SD	4.4	4.1	
SE	1.4	1.0	
Range	31.9 to 46.6	32.2 to 46.7	-5 to +16

No significant difference

Repeats (Table 1A-3b)

Ventilatory and $(dp/dt)_{max.}$ responses to CO_2.

a) No resistance added: 7 subjects repeated the test once, and 1 subject twice. It was found that the coefficient of variation was small for ventilatory (mean 9.0%) and $(dp/dt)_{max.}$ (mean 11.0%) response to CO_2.

b) Added Resistance: 3 subjects repeated the test once. The mean coefficient of variation was 8.0% for ventilation and 8.0% for $(dp/dt)_{max.}$ response.

PCO_2 (mm.Hg)	$\dot{V}_E$ (L min^{-1})	$P_{0.1}$ (cm. H_2O)
48.1	8.85	1.4
53.3	12.50	4.3
56.2	18.90	6.1
57.3	26.29	9.1
60.9	29.23	9.9
63.4	36.20	11.1
64.6	44.89	13.8
67.4	60.14	15.0
69.1	68.30	16.1

Subject 1-39

Table 1A-4. Experimental data during CO_2 rebreathing in one subject.

Subjects.	Ventilatory response.	B	$P_{0.I}$ response.	y intercept.
I-25	I.I5	40.9	0.2I	- 9.99
I-27	3.I0	38.8	0.85	-35.77
I-3I	I.57	39.8	0.I6	- 9.05
I-40	3.54	44.3	0.87	-36.77
I-37	I.I3	35.5	0.32	-I0.50
I-4	2.95	45.6	0.6I	-29.40
I-36	2.70	38.9	I.I0	-38.75
I-34	I.45	39.4	0.32	-I0.50
I-29	2.46	43.7	0.65	-30.3I
I-30	2.73	44.8	0.56	-28.75
I-I4	3.6I	45.7	I.02	-39.45
I-8	I.44	38.3	0.54	-25.7I
I-2I	2.40	39.4	0.84	-36.7I
I-I9	I.68	43.4	0.56	-27.4I
I-28	2.83	40.4	0.85	-37.70
I-26	2.75	4I.7	0.9I	-39.88
I-5	2.95	38.3	0.73	-34.35
I-39	2.85	48.I	0.72	-33.38
I-40	2.35	39.I	0.74	-37.63
I-II	2.I0	40.I	0.3I	-I2.35
Mean	2.39	4I.3	0.64	-27.30
SD	0.76	3.2	0.27	II.34
SE	0.I7	0.7	0.06	2.60

$\Delta \dot{V}_E / \Delta PCO_2$ ventilatory response to CO_2. litres $min.^{-I} mm.Hg.^{-I}$

B intercept on x axis of CO_2 ventilatory response slope. $(mm.Hg)^2$

$\Delta P_{0.I} / \Delta PCO_2$ $P_{0.I}$ response to CO_2. $cm.H_2O\ mm.Hg^{-I}$

y intercept. intercept on y axis of $P_{0.I}$ response to CO_2. $cm.\ H_2O$

Table IA-5a. Results of CO_2 rebreathing test, showing ventilatory and $P_{0.I}$ responses.

Table 1A-5b.

Repeats on $P_{0.1}$ and ventilatory responses to CO_2.

Subjects	$\Delta \dot{V}E/\Delta PCO_2$	$\Delta P_{0.1}/\Delta PCO_2$
1-25	1.15	0.21
	1.35	0.25
1-4	2.95	0.61
	3.40	0.70
1-11	2.10	0.31
	1.85	0.28
	2.30	0.35

Absolute mouth occlusion pressure change at 0.1 second ($P_{0.1}$) response to CO_2. (Table 1A-5a)

20 subjects underwent CO_2 response test using both ($P_{0.1}$) and ventilation simultaneously as measured responses to CO_2. The range of ventilatory response to CO_2 was from 1.13 to 3.54 L min^{-1} $mm.Hg.^{-1}$. (mean 2.39)
B ranged from 35.5 to 48.1 mm.Hg. (mean 41.3)
When CO_2 response is measured in terms of ($P_{0.1}$), the range was from 0.21 to 1.10 $cm.H_2O$ $mm.Hg.^{-1}$. (mean 0.64)
The y axis intercept on the ($P_{0.1}$) response slope ranges from -9.05 to -39.88 $cm.H_2O$ (mean -27.30)

Repeats. (Table 1A-5b)

2 subjects repeated the test once and 1 subject twice. The mean coefficient of variation for ventilatory response was 10.0% and for ($P_{0.1}$) response was 10.0%.

($P_{0.1}$) and ventilatory response to CO_2 correlation

There was a highly significant correlation between ($P_{0.1}$) and ventilatory response to CO_2 in all the 20 subjects tested.
($r = 0.807$ $p < 0.001$) See Fig. 1A-7.

Subject 1-4

PAO_2 (mm.Hg.)	$\frac{1}{PAO_2-32}$	$\dot{V}_E$ ($L.min^{-1}$)	(dp/dt) max. ($cm.H_2O\ sec^{-1}$)
114.1	0.012	10.20	12.48
101.2	0.014	10.64	12.71
92.7	0.016	11.32	13.10
82.7	0.020	12.52	13.35
74.1	0.024	12.00	14.25
64.1	0.031	13.50	15.10
57.0	0.040	15.50	18.77
49.9	0.056	20.20	21.72
42.8	0.093	27.10	30.20
39.2	0.138	43.20	45.60

Table. 1A-6. Experimental data during isocapnic hypoxia test in one subject.

Subjects.	$\Delta \dot{V}_E / \Delta PCO_2$	$\frac{\Delta \dot{V}_E}{\Delta (1/PAO_2 - 32)}$	$\frac{\Delta (dp/dt)_{max.}}{\Delta (1/PAO_2 - 32)}$	$\dot{V}O$	y intercept.
1-15	2.12	122.8	112.8	8.6	12.7
1-26	2.38	174.1	236.7	9.9	18.1
1-27	3.15	182.3	253.0	11.4	5.2
1-28	2.40	104.0	89.1	11.3	16.1
1-13	2.61	164.1	179.8	10.6	6.6
1-29	2.21	173.6	222.0	12.5	12.7
1-30	2.97	196.9	191.0	8.5	14.8
1-31	1.44	92.3	98.6	9.9	15.0
1-32	2.43	186.7	181.0	7.8	10.9
1-33	1.85	130.3	113.8	9.7	9.6
1-34	1.53	115.0	123.5	7.2	18.6
1-35	1.11	84.1	77.5	9.1	8.4
1-25	1.40	86.6	84.7	7.9	17.0

Table IA-7a Results of isocapnic hypoxia test, showing ventilatory and $(dp/dt)_{max.}$ responses.

Table IA-7a (contd)

Subjects.	$\Delta \dot{V}_E / \Delta PCO_2$	$\frac{\Delta \dot{V}_E}{\Delta (I/PAO_2 - 32)}$	$\frac{\Delta (dp/dt)_{max.}}{\Delta (I/PAO_2 - 32)}$	$\dot{V}O$	y intercept
I-36	2.90	I84.8	253.0	8.8	I4.0
I-I4	3.67	2I9.5	235.5	7.9	I4.5
I-4	3.I3	250.3	257.I	6.6	8.3
I-22	3.70	203.7	2II.0	9.9	I3.8
I-37	I.I3	II3.9	I58.5	II.7	I3.0
I-I9	2.I5	I43.9	I28.6	9.I	2I.5
I-38	I.07	98.6	98.5	9.0	I5.2
Mean	2.27	I5I.4	I65.3	9.3	I3.7
SD	0.82	48.7	63.9	I.5	4.I
SE	0.I8	I0.9	I4.3	0.3	0.9

Table IA-7a. Units used.

$\Delta \dot{V}_E / \Delta PCO_2$	ventilatory response to CO_2 litres min^{-I} $mm.Hg.^{-I}$
$\frac{\Delta \dot{V}_E}{\Delta (I/PAO_2 - 32)}$	Parameter A, measurement of ventilatory response to hypoxia. litres $mm.Hg.min^{-I}$
$\frac{\Delta (dp/dt)_{max.}}{\Delta (I/PAO_2 - 32)}$	Parameter 'A $(dp/dt)_{max.}$', measurement of $(dp/dt)_{max.}$ response to hypoxia. $cm.H_2O$ mm.Hg. sec^{-I}
$\dot{V}O$	y intercept of parameter A slope. $litres.min^{-I}$
y intercept.	y intercept of parameter 'A $(dp/dt)_{max.}$' slope. $cm.H_2O.$ sec^{-I}

Table 1A-7b.

Repeats of hypoxic response tests.

Subjects	$\frac{\Delta \dot{V}_E}{\Delta (1/PAO_2 - 32)}$	$\frac{\Delta (dp/dt)_{max.}}{\Delta (1/PAO_2 - 32)}$
1-26	174.1	236.7
	198.1	275.0
1-30	196.9	191.0
	170.0	170.5
1-31	92.3	98.6
	101.4	85.1

Response to hypoxia. (Table 1A-7a)

20 subjects who underwent the CO_2 response tests also underwent the isocapnic hypoxia test. Hypoxic drive was measured both in terms of ventilatory and $(dp/dt)_{max.}$ changes.

The ventilatory response to CO_2 in the 20 subjects studied ranged from 1.11 to 3.70 L min^{-1}mm.Hg. (mean 2.27).

When ventilatory response to hypoxia was measured and given as parameter A, $\frac{\Delta \dot{V}_E}{\Delta (^1/PAO_2-32)}$, the range was from 84.1 to 250.3 (mean 151.4).

$\dot{V}_0$ for ventilatory response to hypoxia ranged from 6.6 to 12.5 L min^{-1} (mean 9.3).

When hypoxic response was measured as $(dp/dt)_{max.}$ change, expressed as parameter 'A $(dp/dt)_{max.}$', $\frac{\Delta (dp/dt)_{max.}}{\Delta (^1/PAO_2-32)}$, the range was from 77.5 to 253.0 (mean 165.3).

y intercept for $(dp/dt)_{max.}$ hypoxic response ranged from 5.2 to 21.5 L min^{-1}. (mean 13.7).

Correlation between $(dp/dt)_{max.}$ response and ventilatory response to hypoxia

There is a significant correlation between $(dp/dt)_{max.}$ response and ventilatory response to hypoxia in all the subjects studied.

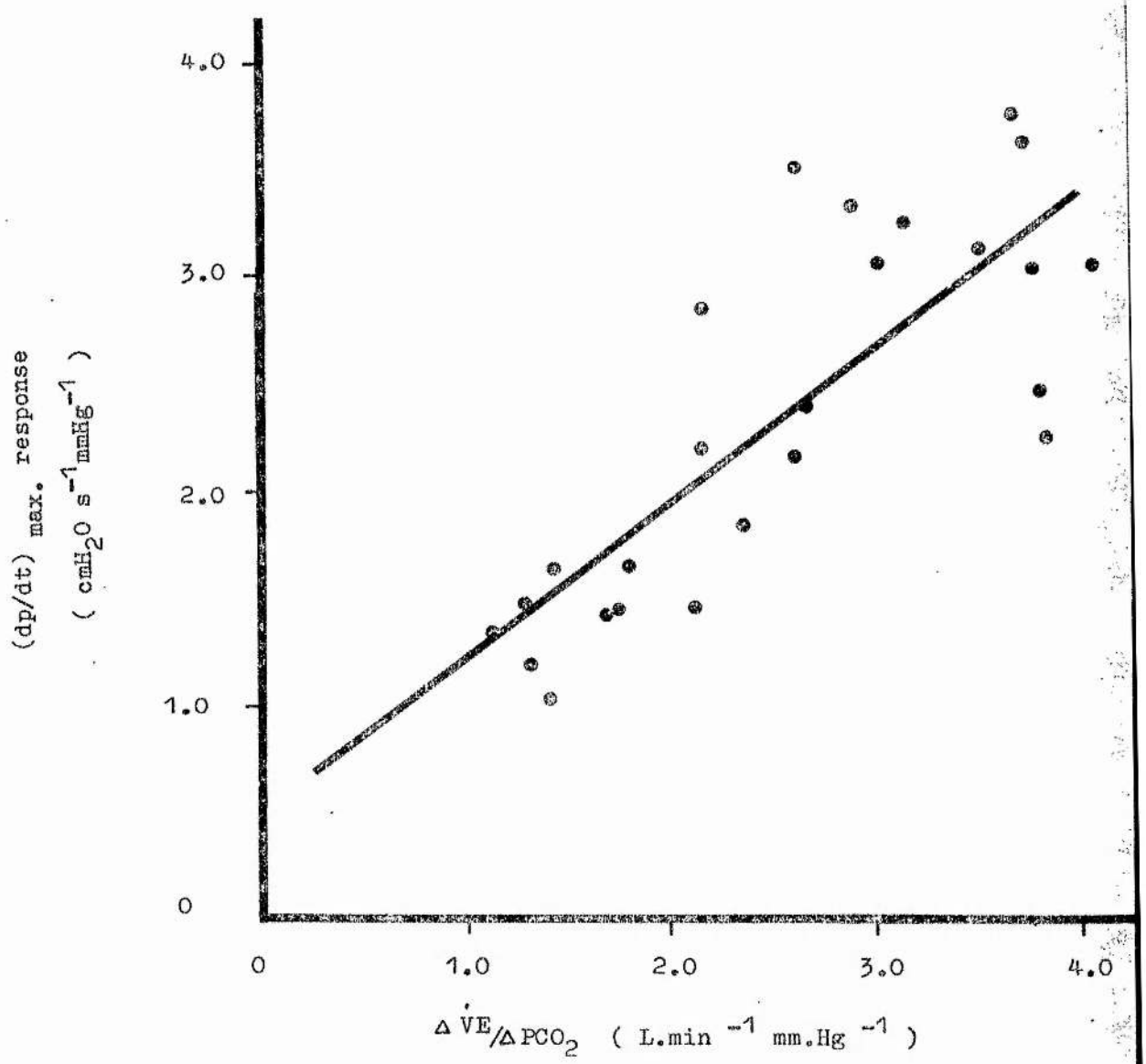
($r = 0.905$ $p = <0.001$) (Fig. 1A-12, 2-14 Table 1A-7a).

Correlation between hypoxic and hypercapnic responses

Ventilatory response to hypercapnia correlate significantly with $(dp/dt)_{max.}$ response to hypoxia ($r = 0.775$ $p = <0.001$) and with ventilatory response to hypoxia ($r = 0.881$ $p = < 0.001$) Table 1A-7_a (Fig. 1A-13).

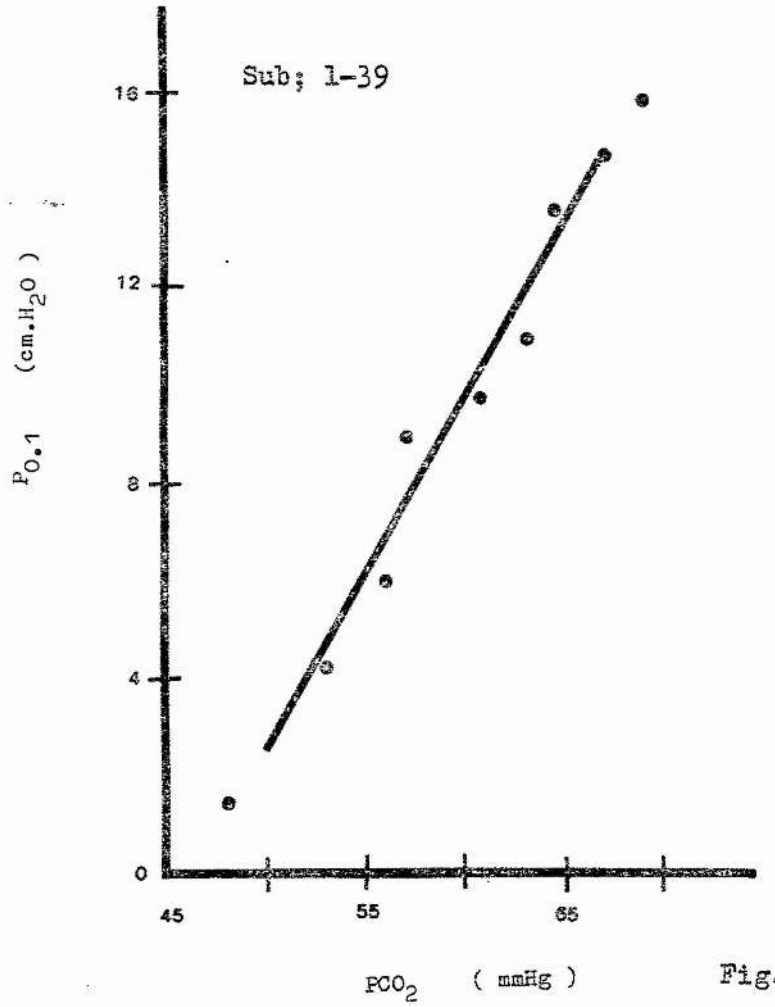
Repeats (Table 1A-7b).

3 subjects repeated the test once. The mean coefficient of variation for parameter 'A' was 9.0% and for parameter 'A $(dp/dt)_{max.}$' was 9.5%.



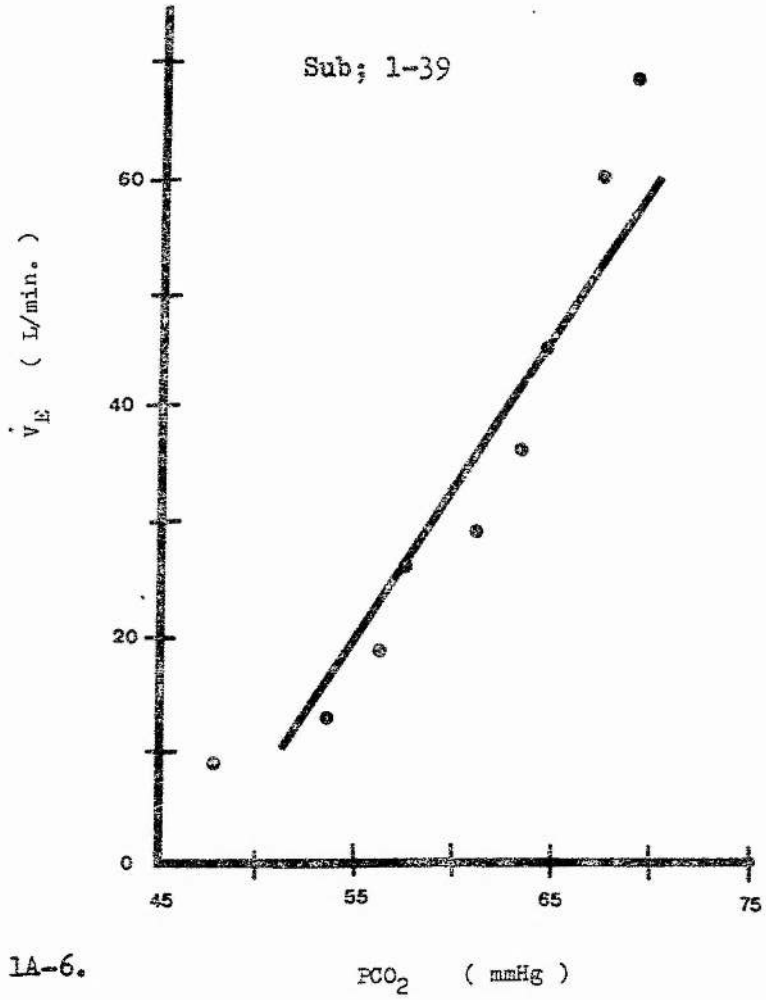
Fig; 1A-5 Correlation between ventilatory and $(^{dp}/dt)$ max. responses to CO_2 in 25 subjects (normals). Each point represents one subject.

r = 0.814 p = < 0.001



Graph showing occluded mouth pressure ($P_{0.1}$) plotted against CO_2 tension in a representative subject.

Fig. 1A-6.



Graph showing ventilation plotted against CO_2 tension in a representative subject.

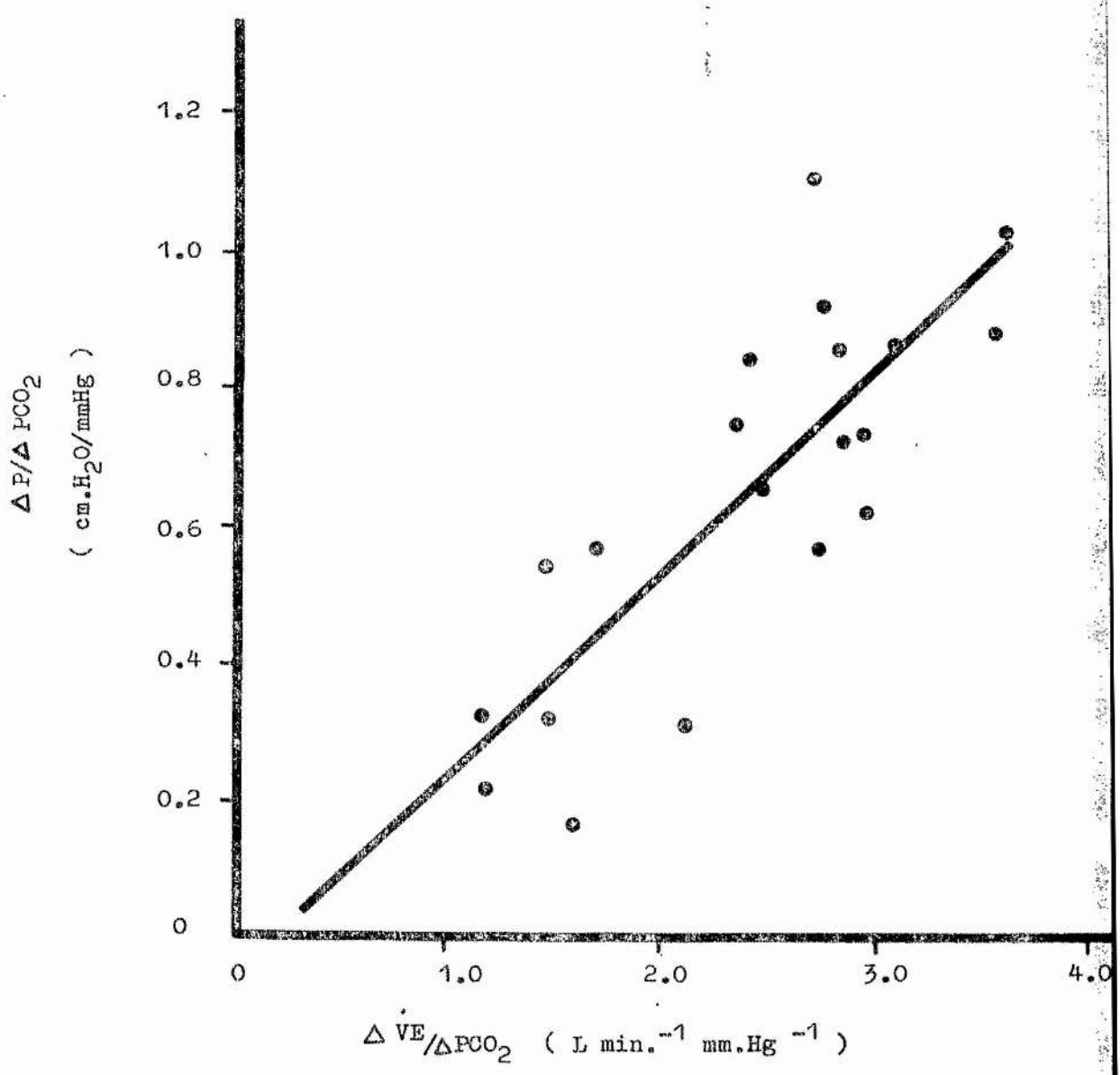


Fig: 1A-7 Correlation between ventilatory and mouth occlusion pressure responses to CO_2 in 20 subjects (normals). Each point represents one subject.
r = 0.807 p = < 0.001

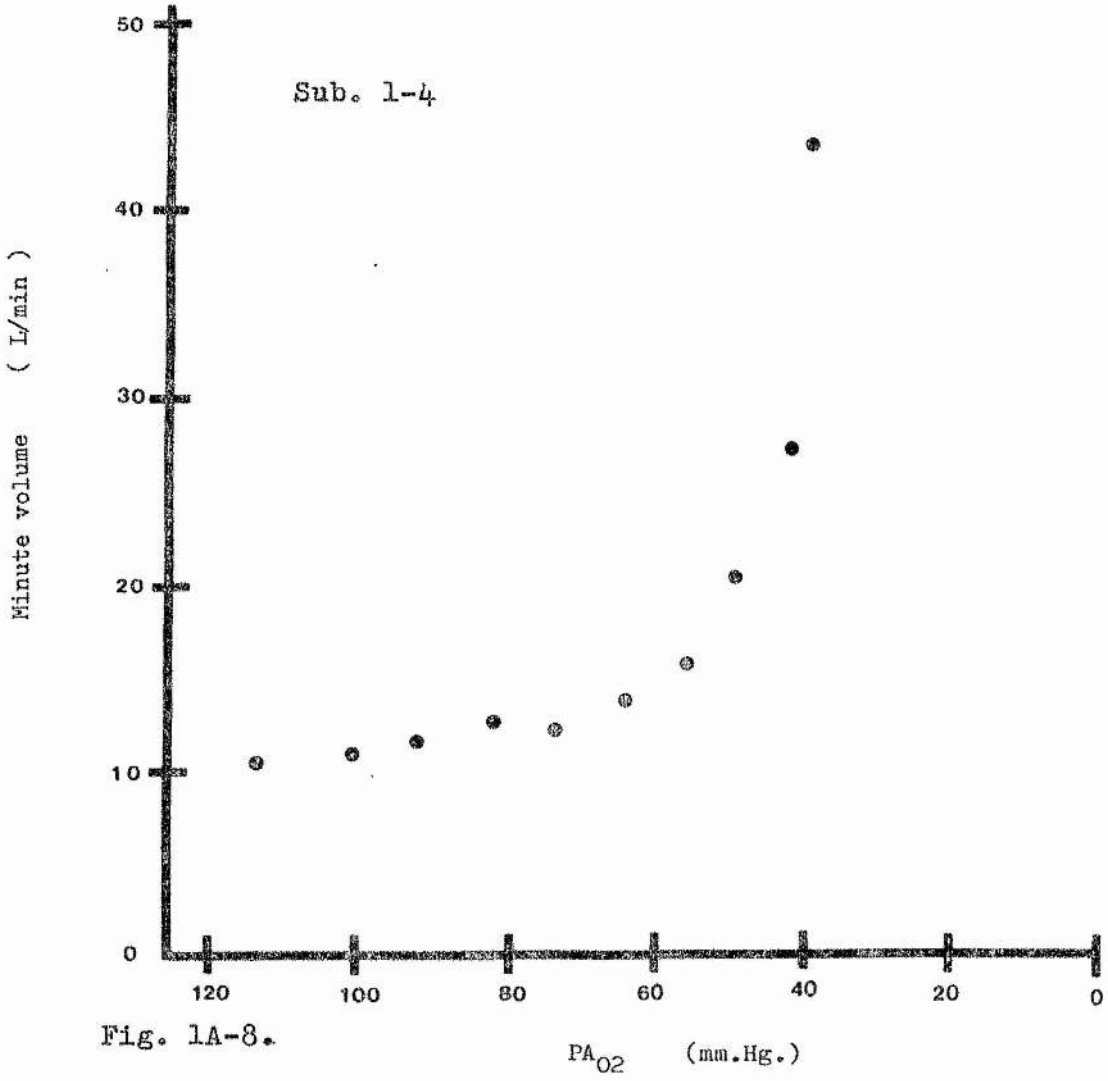


Fig. 1A-8.

Graph showing ventilation plotted against PO_2 in a representative subject, at a steadily maintained P_{CO2}.

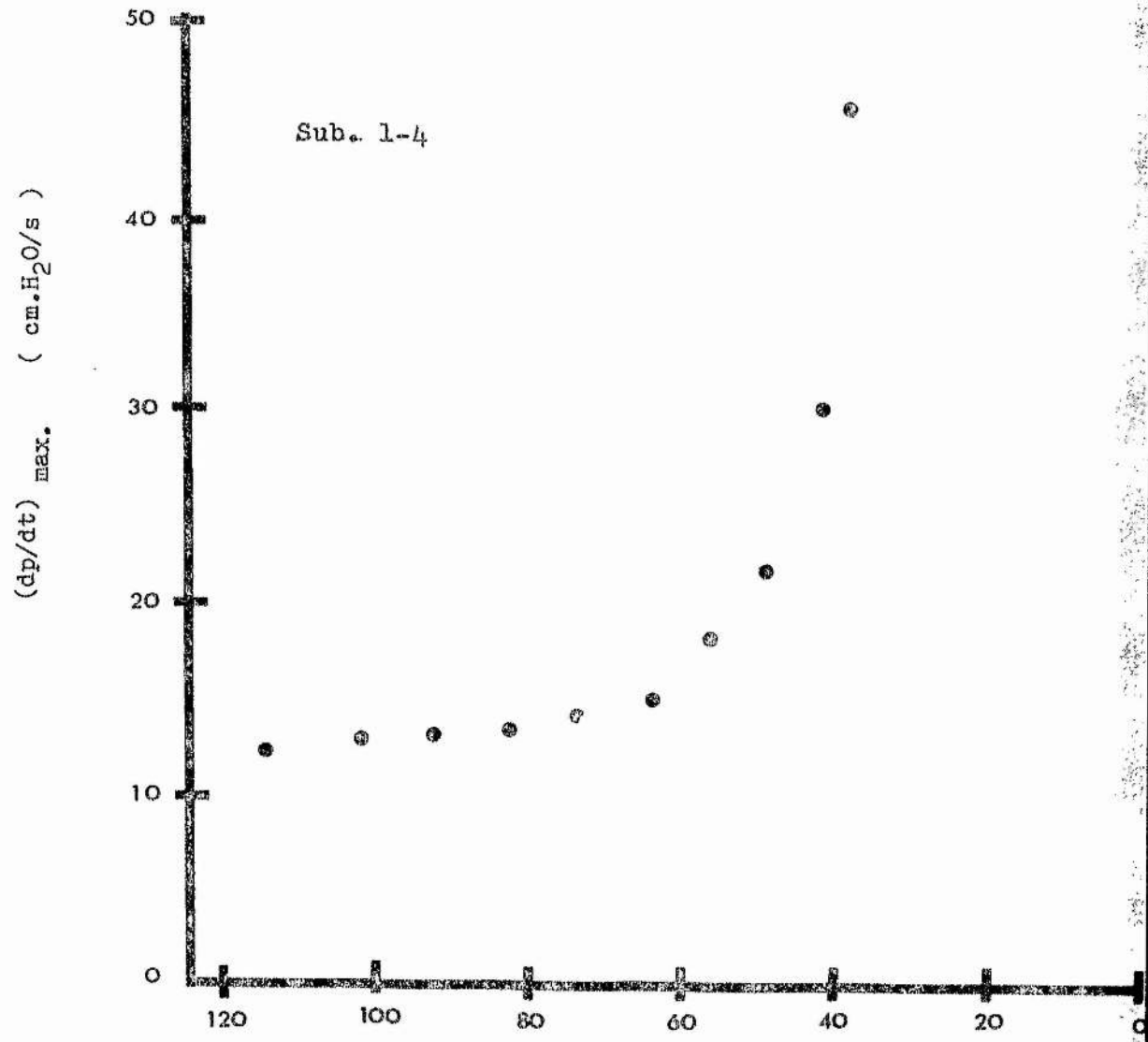


Fig. 1A-9.

Graph showing $(dp/dt)_{max.}$ plotted against PO_2 in a representative subject, at a steadily maintained P_{CO2}.

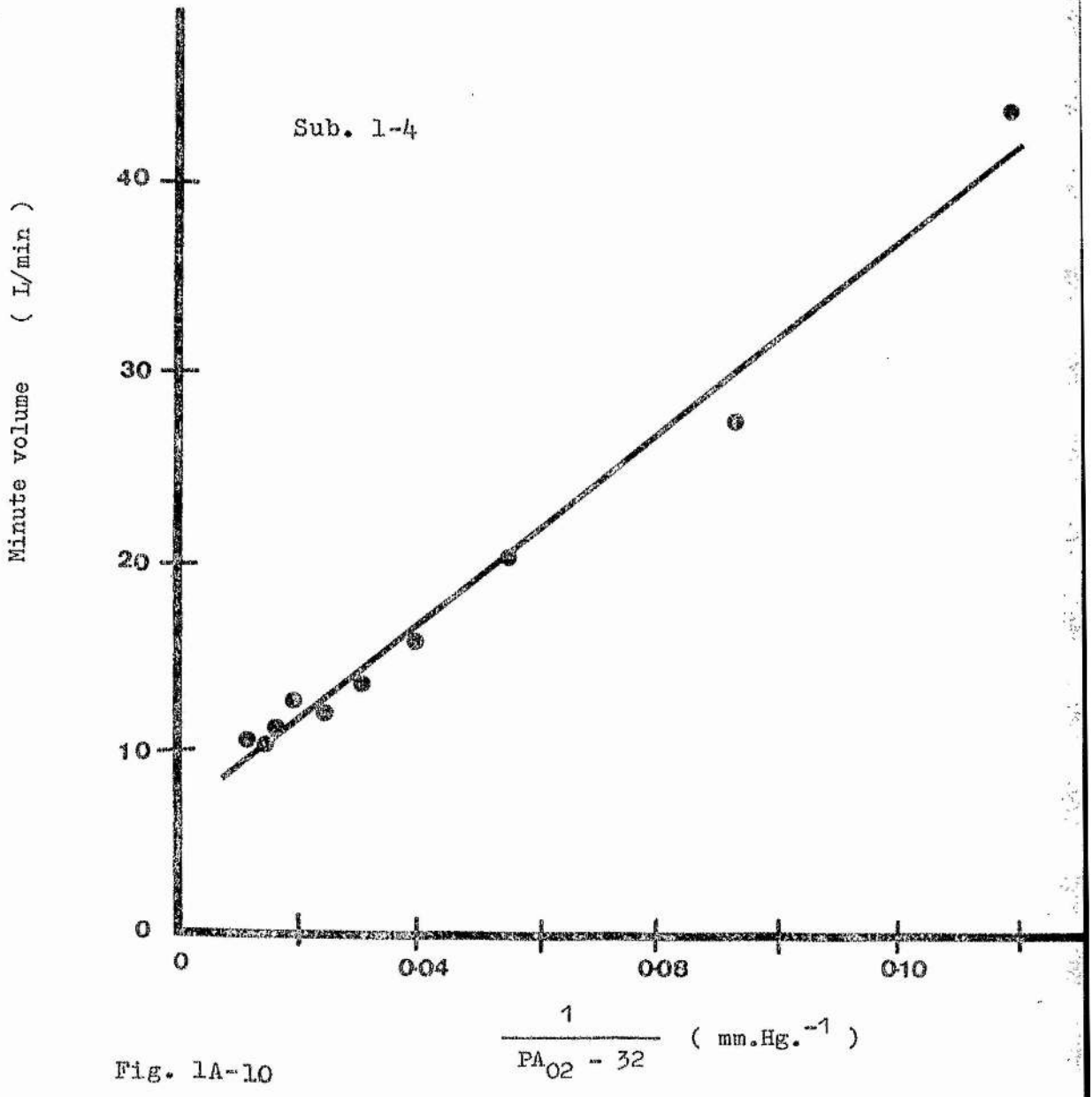


Fig. 1A-10

Graph showing ventilation plotted against the reciprocal of PA_{O2}-32, in a representative subject, at a steadily maintained P_{CO2}.

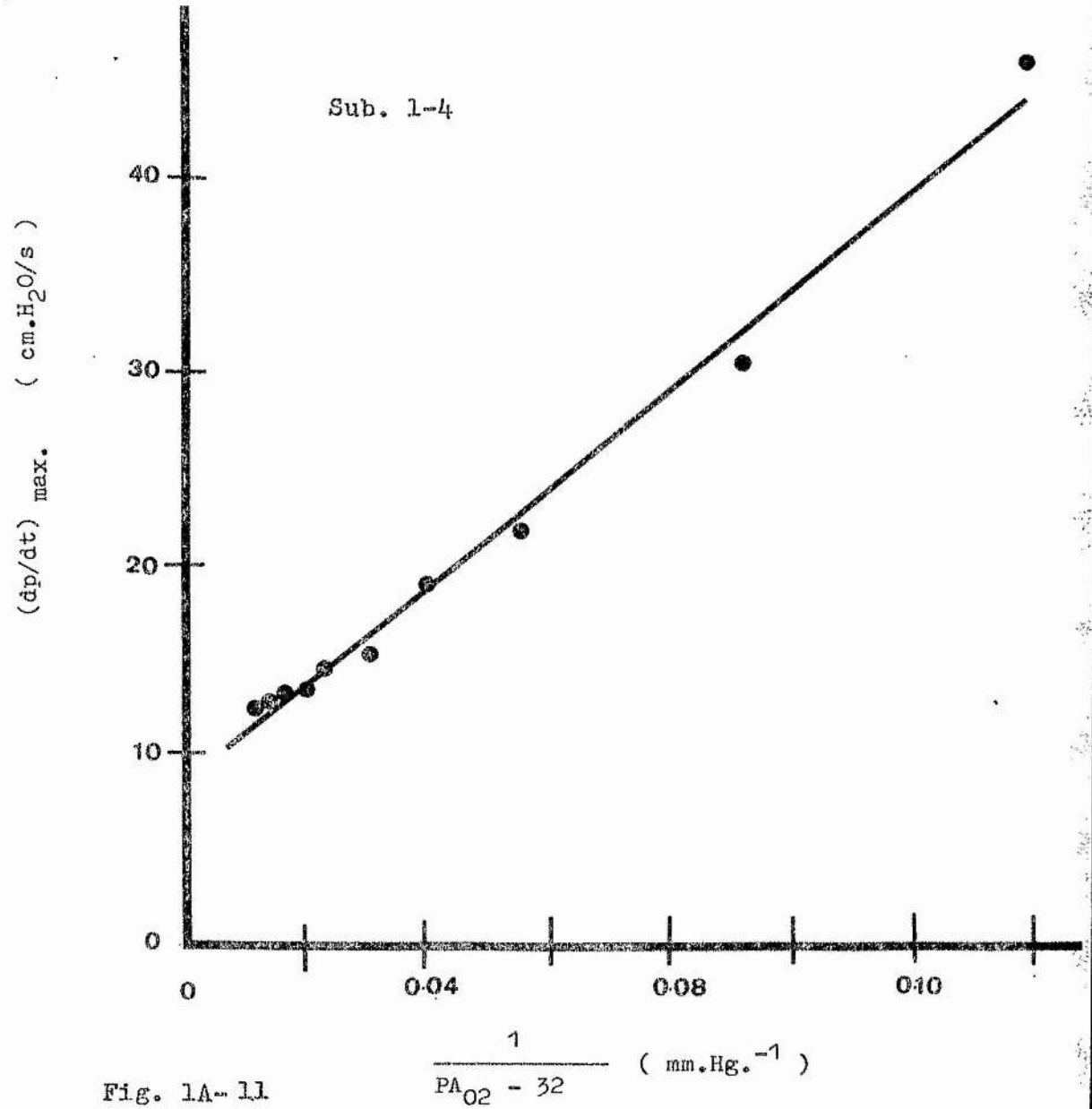


Fig. 1A-11

Graph showing $(dp/dt)_{max.}$ plotted against the reciprocal of PA_{O2}-32, in a representative subject, at a steadily maintained P_{CO2}.

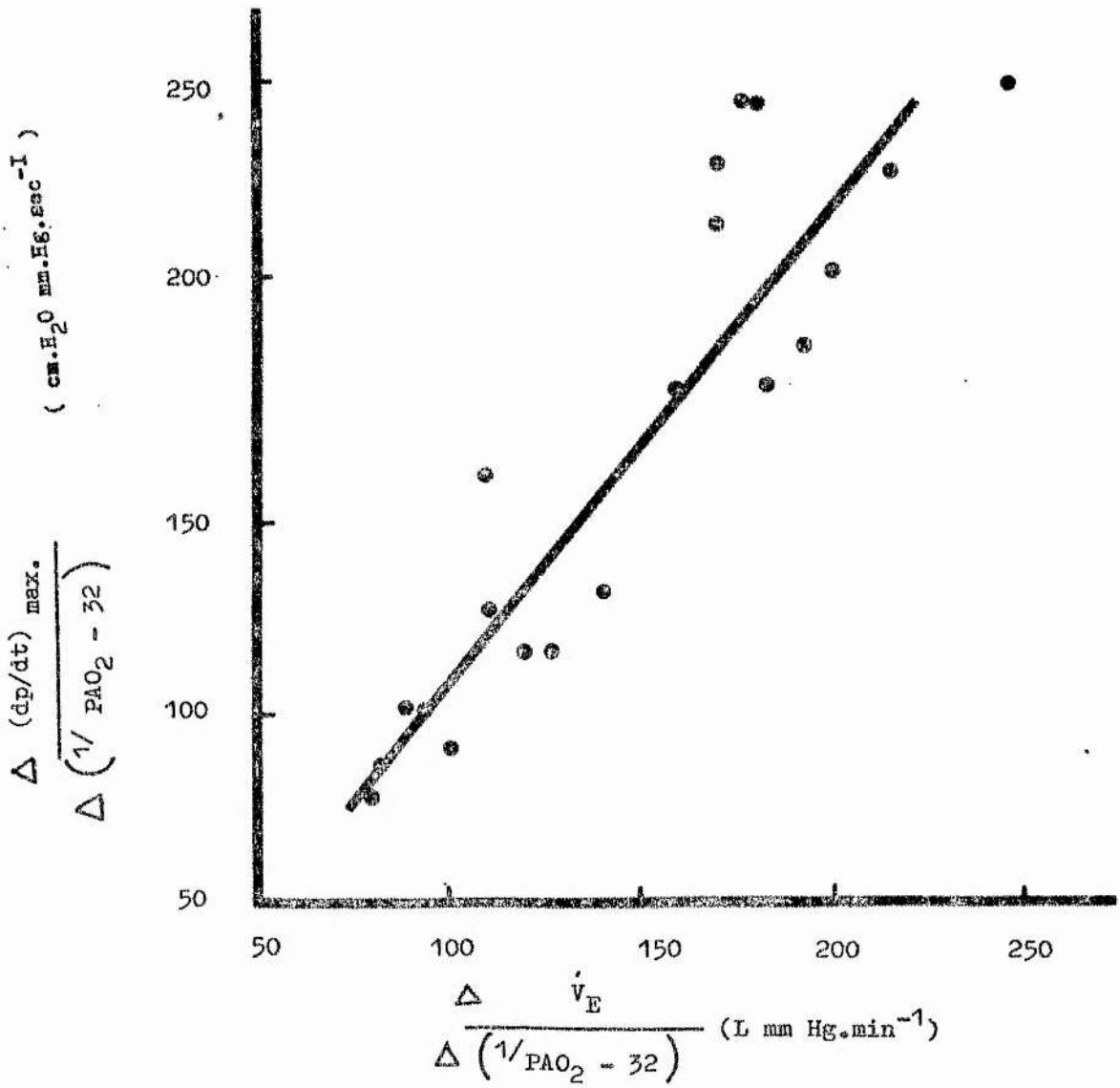


Fig. 1A-12.
Relationship between $(dp/dt)_{max.}$ and ventilatory responses to hypoxia in 20 subjects.

r= 0.905
p= < 0.001

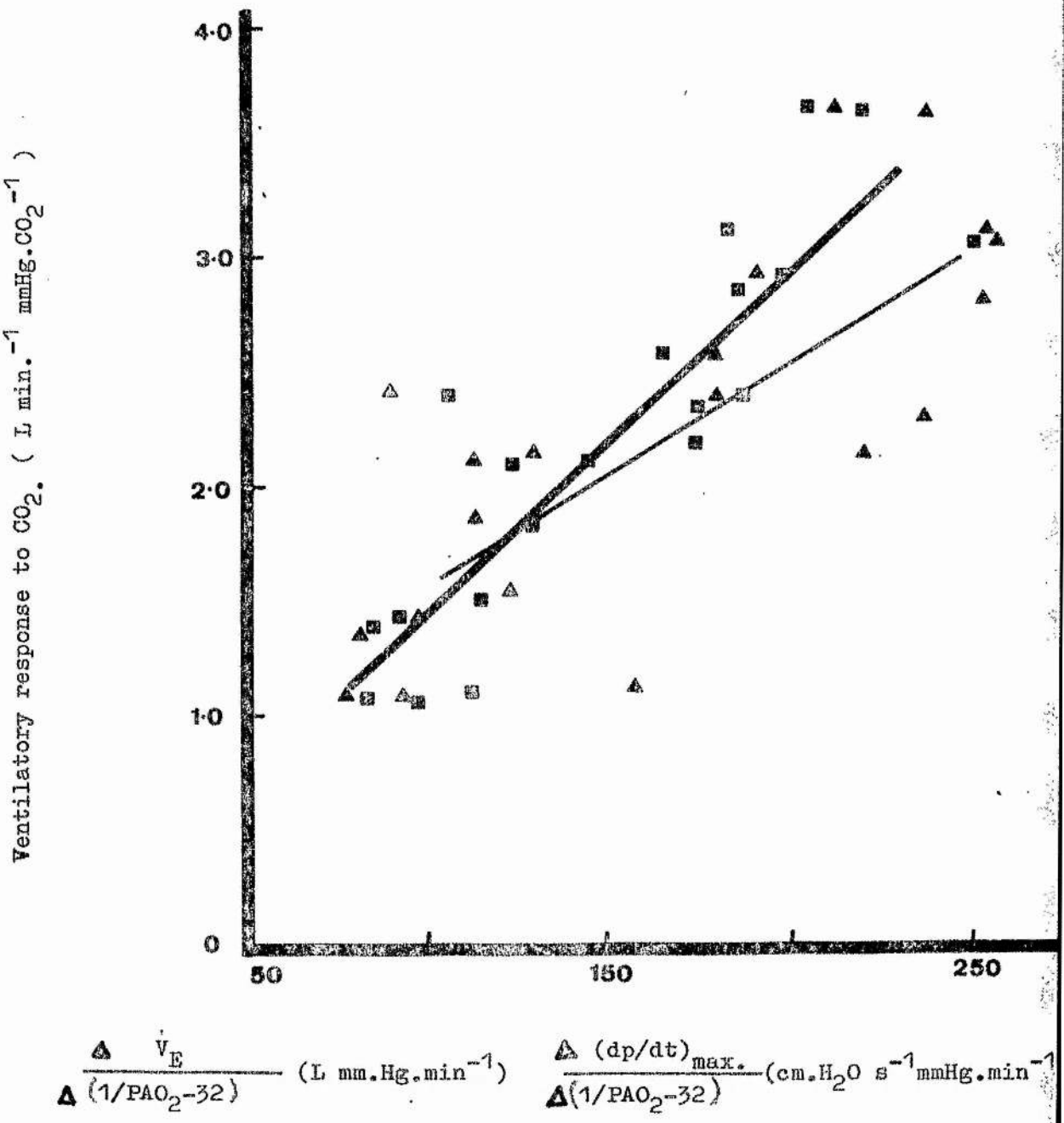


Fig.1A-13. Relationship between ventilatory response to CO_2 and $(dp/dt)_{max.}$ and ventilatory response to isocapnic hypoxia.

▪▪▪▪ ■ ventilatory response to hypoxia r=0.881 p=<0.001

——▲ $(dp/dt)_{max.}$ response to hypoxia r=0.775 p=<0.001

Representative individuals' results. Normals.

Ventilatory and $(dp/dt)_{max.}$ responses to CO_2.

Subject 1-1 Data table 1A-2 .

Fig. 1A-2 shows the close relationship between ventilation and $(dp/dt)_{max.}$ changes with rising PCO_2. This relationship was demonstrated in all the normals tested. Individual regression coefficient for each curve was greater than 0.90 for all the normals tested.

The Figs. 1A-3 and 1A-4 showed that whilst $(dp/dt)_{max.}$ response did not show any significant change with airways restriction, there was significant reduction in ventilatory response slopes with restriction.

Ventilatory and $(P_{0.1})$ response to CO_2.

Subject 1-39 Data Table 1A-4

Fig. 1A-6

The figure showed the linear relationship between $(P_{0.1})$ with increasing PCO_2. Similar relationship was shown between ventilation and increasing PCO_2. In all the subjects tested, each individual slope (both $(P_{0.1})$ and ventilation) showed a regression coefficient of over 0.90.

$(dp/dt)_{max.}$ and ventilatory responses to hypoxia

Subjects 1-4 Data Table 1A-6

Figs. 1A-8, 9, 10, 11.

The figures above showed the hyperbolic relationship exhibited when $(dp/dt)_{max.}$ and ventilation were plotted against decreasing PO_2. When $(dp/dt)_{max.}$ and ventilation were plotted against the reciprocal of PO_2, straight line relationships were obtained, slopes of which gave the parameter "A" and parameter "A $(dp/dt)_{max.}$". These slopes gave an indication of hypoxic drive, where the bigger the A value, the greater the hypoxic drive.

DISCUSSION

Normal subjects

Ventilatory and $(dp/dt)_{max.}$ response to CO_2.

There was a significant correlation between ventilatory and $(dp/dt)_{max.}$ response to CO_2 in the normal subjects tested. Repeats show small and similar variations for both the responses measured. This suggests that $(dp/dt)_{max.}$ is as reliable an index as ventilation of respiratory centre output during hypercapnia in unobstructed breathing.

There was a significant reduction (mean 47%) in ventilatory response to CO_2 in normal subjects in the presence of added airways resistance when compared with unobstructed CO_2 breathing. This is in accordance with the general findings of reduction in CO_2 ventilatory response with added airways obstruction (Cherniak and Snidal 1956, Eldridge and Davis 1959 and Matthews and Howell 1975); supporting the suggestion that airways obstruction may cause this reduction.

However, when CO_2 response was measured in terms of $(dp/dt)_{max.}$ response, there was no significant reduction in the response with added airways obstruction when compared with free CO_2 breathing, which agrees with the findings of Matthews and Howell 1975. This suggests that whilst ventilatory response to CO_2 may be affected by airways resistance, $(dp/dt)_{max.}$ response is independent of resistance.

($P_{0.1}$) response

The study of ($P_{0.1}$) was done to assess whether it was a reliable measurement of CO_2 responsiveness. It was found that ($P_{0.1}$) increases with increase in PCO_2. These findings were in general agreement with Whitlaw et al., 1975 who found a curvilinear relationship between ($P_{0.15}$) and the level of PCO_2. The findings here showed a linear relationship between ($P_{0.1}$) and PCO_2 which was similar to the findings of Altose et al., 1976. The significant correlation between the total mouth occlusion pressure and the ventilatory responses to CO_2 (Fig. 1A-7), showed that it is a reliable method for assessing the respiratory chemosensitivity. Results obtained by other workers using similar tests are as follows:-

Workers	Response	Subjects	$P_{0.1}$ response ($cm.H_2O$ $mm.Hg.^{-1}$)
Kryger et al 1975	$P_{0.1}$	9	Range 0.18 to 0.82
Lopata et al 1977	$P_{0.15}$	7	Range 0.31 to 1.25
Derenne et al 1976	$P_{0.1}$	6	Range 0.17 to 0.62
Maranetra and Pain 1974	$P_{0.3}$	12	Mean 0.95 SD 0.5
Altose et al 1976 [a]	$P_{0.1}$	16	Mean 0.88 SE 0.14
Present study	$P_{0.1}$	20	Mean 0.64 SE 0.06

The intercept on "y" axis on $P_{0.1}$ response slope ranges from -9.05 to -39.88 $cm.H_2O$ (mean -27.30 SD 2.60) was comparable to that found by Altose et al 1976 [a] (mean -33.41 SE 6.20).

Comparison between $(dp/dt)_{max.}$ and $P_{0.1}$ responses to CO_2.

Both the responses measured gave similar results. However, it seems from the experiments carried out, that $(dp/dt)_{max.}$ has a practical advantage over $P_{0.1}$. This is due to the fact that during manual airways occlusion $P_{0.1}$ measurement, despite all precautions taken, conscious anticipation by the subjects tends to have some bearing on the results. However, this does not reflect the unreliability of the method. Further modification, such as electrical random occlusion of the airways, would overcome this disadvantage.

On the other hand, $(dp/dt)_{max.}$ measurement seems to be more practical and simpler to use as the transient occlusion provided by the valves in the mouthpiece, required no manual handling.

Because the subjects were not aware of the transient occlusion and so did not voluntarily change their respiration during the rebreathing period. In all the subjects studied during the $(dp/dt)_{max.}$ studies, none felt any increased resistance to inspiration. Whereas during the total occlusion pressure tests, subjects did notice the inspiratory occlusion. Thus the practical advantage of $(dp/dt)_{max.}$ response test over the total occlusion pressure measurement, made $(dp/dt)_{max.}$ the favourable choice for further testing.

$(dp/dt)_{max.}$ as a hypoxic drive index.

In this study, during isocapnic hypoxia, $(dp/dt)_{max.}$ increased with decreasing O_2, the relationship being hyperbolic. When $(dp/dt)_{max.}$ was related to the reciprocal of PO_2, a straight line relationship was obtained.

A similar hyperbolic relationship was demonstrated between ventilation and decreasing PO_2, and a straight line relationship was obtained when ventilation was plotted against the reciprocal of PO_2 (parameter A of Weil et al 1970).

When the slopes of parameter "A", $\Delta\dot{V}E/\Delta(1/PAO_2 - 32)$ and parameter "A $(dp/dt)_{max.}$", $\Delta dp/dt_{max.}/\Delta(1/PAO_2 - 32)$ were compared, the significant correlation between the two showed that $(dp/dt)_{max.}$ changes paralleled changes in ventilation during isocapnic hypoxia. Thus $(dp/dt)_{max.}$ may be a reliable index of respiratory motor output.

To test whether the $(dp/dt)_{max.}$ response was repeatable, 3 subjects repeated the test once. The mean coefficient of variation for $(dp/dt)_{max.}$ response to hypoxia was 9.5% and for ventilatory response was 9%. This shows that the repeatability for both responses was similar and since variation was small, $(dp/dt)_{max.}$ is a reliable response to hypoxia index.

There was a significant correlation between ventilatory response to CO_2 and both $(dp/dt)_{max.}$ and ventilatory response to hypoxia, agreeing with findings by Rebuck et al 1973 and Byrne-Quinn et al 1971 (see Section 2). This again suggests the reliability of $(dp/dt)_{max.}$ as a measure of response to hypoxia.

Steady-state and progressive hypoxia

Essentially there are two main methods used in assessing hypoxic drive in man. These are the steady-state and the changing state methods and their variations. In the steady-state, as employed by Dripps and Comroe 1974 and Jennett 1969a,b, involved breathing from bags containing initially low concentration of oxygen in nitrogen.

Variations of the methods used involved using different concentrations of CO_2.

In the changing-state methods, variations include rebreathing from a bag (Godfrey et al 1971, Rebuck et al 1973) and controlled reduction of inspired oxygen (Weil et al 1970). In this study, the rebreathing method of Rebuck et al 1973 was used. The isocapnic hypoxia test would ensure that the resulting response measured was solely due to oxygen lack. The initial PCO_2 in the rebreathing bag approximates the resting $PaCO_2$.

RESULTS

(Patients)

The patients underwent the same CO_2 ventilatory and $(dp/dt)_{max.}$ response tests as the normal subjects. The CO_2 response slopes for the normocapnic patients were mainly obtained for data between 43 and 70 mm.Hg. and for the hypercapnic patients ranging from 55 to 65 up to a maximum of around 85 mm.Hg.PCO_2.

The overall results are given in Tables 1A-8a and 1A-8b.

a) Normocapnic patients

The 37 normocapnic patients tested have a resting $PaCO_2$ of 48 mm.Hg. and less (mean 40). Their FEV_1% ranged from 33 to 82% with a mean value of 51%.

The mean ventilatory response to CO_2 was 0.61 L $min^{-1}mm.Hg^{-1}$ (range 0.06 to 1.35), with the mean B at 12 mm.Hg.

When the response to CO_2 was measured in terms of $(dp/dt)_{max.}$ the mean value was 1.75 cm.H_2O sec^{-1} $mm.Hg.^{-1}$ (range 0.36 to 3.66), and the corresponding x axis intercept at a mean value of 27 mm.Hg.

The resting $(dp/dt)_{max.}$ ranged from 8.0 to 40.66 cm.H_2O sec^{-1} (mean 24.7).

b) Hypercapnic patients

The 12 hypercapnic patients tested have a resting $PaCO_2$ of 50 mm.Hg. and above (range 50 to 60, mean 56 mm.Hg.). The mean FEV_1% was 48.

The mean ventilatory response to CO_2 was 0.27 L $min^{-1}mm.Hg.^{-1}$. (range 0.07 to 0.50), with the mean

Subjects	Age (yrs)	FEV_1/FVC	FEV_1/FVC %	$PaCO_2$ (mmHg)	$\Delta V_E/\Delta PCO_2$ ($L\ min^{-1}mmHg^{-1}$)	B (mmHg)	$\frac{\Delta (dp/dt)_{max.}}{\Delta\ PCO_2}$ ($cm.H_2O\ s^{-1}mmHg^{-1}$)	B_1 (mmHg)	PCO_2[a] (mmHg)	$(dp/dt)_{max.}$[b] ($cm.H_2O\ sec^{-1}$)
Lb.	64	1.30/3.20	43	42	0.71	6.7	1.56	24.6	42.8	35.90
Hst.	63	0.75/1.70	44	46	0.72	17.9	1.53	26.5	46.1	33.10
D. Ush.	61	1.40/3.00	47	37	0.60	28.4	1.08	39.9	42.8	8.00
J. Les	64	1.10/3.10	35	46	0.18	-14.4	0.39	-31.3	47.8	32.60
J. McCal.	55	0.80/1.95	41	39	0.56	21.9	2.80	45.3	50.6	15.00
Nve.	67	0.80/2.10	38	38	0.40	3.6	1.59	29.9	41.3	21.50
D. Mde.	70	2.10/3.50	60	40	0.56	0.6	2.03	36.5	47.7	22.40
Smvle.	58	0.90/1.55	57	40	0.83	21.8	2.87	36.3	42.8	17.60
Fdltn.	70	0.90/1.60	56	43	0.71	14.0	2.71	32.1	49.9	39.80
McNau.	74	0.46/1.65	28	41	0.06	-222.0	1.52	20.4	47.0	35.70
R. Doc.	68	0.60/1.65	36	44	0.37	8.8	1.40	37.2	53.5	25.30
D. Tlr.	72	2.90/4.10	71	37	1.20	19.5	2.17	28.6	42.0	16.80
Al. Ml.	70	1.15/2.65	43	42	0.66	18.0	2.40	37.4	48.0	24.66
J. St.	55	1.50/2.80	54	48	0.26	- 4.8	0.99	23.8	51.0	31.36
J. Ra.	64	0.27/0.90	30	40	0.07	-178.5	0.63	8.9	42.0	21.28
R. Jkn.	64	2.30/3.40	68	40	0.86	21.1	3.09	45.1	45.0	20.53
G. Conn.	66	1.93/2.90	67	40	1.08	23.7	1.52	45.1	45.0	22.64
Al. Ker.	70	2.30/3.10	74	40	1.06	18.0	1.05	30.7	48.0	18.00
Al. Kenn.	70	1.95/2.60	75	38	0.85	8.0	3.66	35.1	41.0	23.00
D. Kl.	59	0.80/1.90	42	44	0.34	-12.9	0.94	17.6	44.0	26.40

Table 1A-8a. Results of CO_2 rebreathing in normocapnic patients, showing ventilatory and $(dp/dt)_{max.}$ responses.

(contd. next table)

Subjects	Age (yrs)	FEV_{1}/FVC	FEV_{1}/FVC %	$PaCO_2$ (mmHg)	$\Delta V_E/\Delta PCO_2$ ($L\ min^{-1} mmHg^{-1}$)	B (mmHg)	$\frac{\Delta (dp/dt)_{max.}}{\Delta PCO_2}$ ($cm.H_2O\ s^{-1} mmHg^{-1}$)	B_1 (mmHg)	$\overline{PCO_2}$[a] (mmHg)	$(dp/dt)_{max.}$[b] ($cm.H_2O\ sec^{-1}$)
N. Br.	50	0.80/2.45	33	41	0.78	25.3	2.48	31.3	48.0	40.66
W. Sut.	63	0.90/1.75	51	39	0.20	-29.4	1.17	20.3	45.0	30.93
J. Morr.	64	1.45/2.05	71	42	0.67	25.8	1.80	27.6	43.0	30.80
R. Ncl.	56	0.90/2.25	40	39	0.53	13.3	1.97	34.8	43.0	20.11
J. Ry.	67	2.25/2.75	82	40	0.82	29.8	1.53	25.9	45.0	31.36
D.Cgl.	65	0.90/2.80	33	39	0.43	8.7	1.78	33.2	47.0	25.60
J. Mgn.	62	0.90/2.00	45	38	0.69	17.4	1.08	20.1	41.0	23.40
St.Tchr.	65	2.60/3.60	72	40	1.35	40.9	2.35	37.2	44.0	21.02
T. Kild.	69	1.90/2.90	65	38	0.88	25.9	1.83	34.1	42.0	18.31
J. Crrgn.	71	1.40/2.80	51	39	0.58	10.6	2.09	30.4	46.0	34.26
D.McD.	52	1.45/2.20	66	38	0.76	24.3	1.82	25.6	40.0	24.37
Al.Ch.	62	0.95/2.43	39	38	0.53	23.9	1.85	37.5	43.0	17.60
A.Bt.	69	0.90/2.35	38	40	0.42	13.2	1.03	27.9	46.0	17.60
R.Forr.	67	1.10/2.07	53	40	0.82	29.0	2.00	36.5	40.0	12.00
J. Step.	69	0.75/1.50	50	40	0.65	23.0	1.46	32.0	43.0	18.20
P. Donn.	69	0.90/1.92	47	40	0.44	3.9	2.25	32.5	46.0	29.68
Lor.	60	0.50/1.50	33	46	0.14	-26.5	0.36	-26.5	53.0	28.00

Table 1A-8a (contd.)

Objects	Age (yrs)	FEV_1/FVC	FEV_1/FVC %	$PaCO_2$ (mmHg)	$\Delta V_E/\Delta PCO_2$ ($L\ min^{-1} mmHg^{-1}$)	B (mmHg)	$\frac{\Delta (dp/dt)_{max.}}{\Delta PCO_2}$ ($cm.H_2O\ s^{-1} mmHg^{-1}$)	B_1 (mmHg)	PCO_2[a] (mmHg)	$(dp/dt)_{max.}$[b] ($cmH_2O\ sec^{-1}$)
PMcB	68	1.40/2.50	56	51	0.45	- 2.7	0.29	-28.1	50.3	23.04
Nor.	68	0.55/1.10	50	51	0.34	4.6	0.36	-63.9	51.9	41.96
W.Ms.	53	1.90/3.00	63	50	0.50	21.3	0.47	20.9	50.6	16.00
S.Gr.	65	0.80/2.50	32	51	0.19	-57.4	0.35	-46.3	52.8	35.56
R.Stup.	60	1.30/3.00	43	50	0.50	18.3	0.50	- 1.4	50.9	26.60
C. Why.	28	2.70/3.20	86	61	0.09	-69.8	0.12	-71.9	62.0	17.00
D. Jst.	60	1.05/2.75	38	54	0.10	-66.2	0.31	-48.4	54.8	33.37
V.Sctt.	54	1.05/2.45	43	56	0.45	15.6	0.40	18.2	56.8	16.00
F.Cosg.	56	0.70/1.65	42	59	0.11	-15.8	0.08	-88.5	60.6	12.44
Rahn	65	0.70/1.90	36	66	0.26	24.21	0.22	1.9	66.5	15.71
Lorn.	61	0.40/1.00	40	63	0.14	-11.1	0.20	-72.3	63.5	27.50
Al.Mit.	65	1.00/1.90	50	60	0.07	-51.2	0.11	-42.8	60.2	11.20

Table 1A-8b. Results of CO_2 rebreathing in hypercapnic patients showing ventilatory and $(dp/dt)_{max.}$ responses.

Tables 1A-8a and 1A-8b. explanations on some units used.

B_1 intercept on x-axis of $(dp/dt)_{max.}$ response to CO_2 slope.

PCO_2^a approximate bag PCO_2 where 'resting' $(dp/dt)_{max}$ measurement is taken.

$(dp/dt)_{max.}^b$ 'resting' $(dp/dt)_{max.}$ value.

B at -15.8 mm.Hg.

The mean $(dp/dt)_{max.}$ response to CO_2 was 0.28 $cm.H_2O\ sec^{-1}mm.Hg^{-1}$ (range 0.08 to 0.47), and the corresponding x axis intercept at a mean value of -15.8 mm.Hg.

The mean resting $(dp/dt)_{max.}$ was 23 $cm.H_2O\ sec^{-1}$ (range 11.2 to 41.9).

Age.

The age of all the chronic bronchitic patients ranged from 52 to 74 years (mean 63.7). The mean age of the normocapnic bronchitics was 64 and for the hypercapnic bronchitics, 61.3 years old.

There was no significant difference between the mean age of the two groups.

One hypercapnic patient, aged 28 years, was not included in the age analysis as he did not have chronic obstructive airways disease.

Resting $(dp/dt)_{max.}$ levels.

There was no significant difference between the resting $(dp/dt)_{max.}$ levels between the normocapnic and hypercapnic groups.

Individual Cases

Representative Normocapnic Patient

Patient A.Bt. Fig. 1A-14 Table 1A-9.

This patient had a severe airways obstruction with an FEV_1/FVC of only 38%. His ventilatory response to CO_2 was slightly low at 0.42 L $min^{-1}mm.Hg.^{-1}$. However, his $(dp/dt)_{max.}$ response of 1.03 $cm.H_2O$ sec^{-1} $mm.Hg^{-1}$ was within range of those found in the study of normals. With his resting $PaCO_2$ also being normal, it can be suggested that his respiratory drive to CO_2 as measured by his ventilatory response was not truly shown as it was limited by the obstruction. However, his CO_2 drive can be assessed quite accurately by his $(dp/dt)_{max.}$ response.

Representative Hypercapnic Patients

Patient Al.Mit. Fig. 1A-15 Table 1A-10

This patient has an FEV_1/FVC of 57% which was not too severe. However, his ventilatory response to CO_2 (0.07 L $min^{-1}mm.Hg^{-1}$) was the lowest found in the hypercapnic group. His $(dp/dt)_{max.}$ response too was one of the lowest in the group (0.11 cmH_2O $sec^{-1}mm.Hg^{-1}$). This would suggest that he had a reduced CO_2 respiratory drive, probably due to his CO_2 retention.

Patient C.Why. Fig.1A-16 Table 1A-10.

This patient had a high resting $PaCO_2$ (at 61 mm.Hg.) but a normal FEV_1/FVC of 86%. This may be due to pulmonary shunting, leading to CO_2 retention. Both his ventilatory response (0.09 L $min^{-1}mm.Hg.^{-1}$) and $(dp/dt)_{max.}$ response

Subject A.Bt.

PCO_2 (mm.Hg.)	$\dot{V}_E$ ($L.min^{-1}$)	$(dp/dt)_{max.}$ ($cm.H_2O\ sec^{-1}$)
46.7	12.04	17.60
49.2	16.43	23.54
52.4	16.07	24.60
54.5	17.46	29.48
57.7	19.89	31.20
60.6	20.15	33.60
62.0	21.96	35.88
64.1	22.11	35.40
68.4	20.92	42.60

Table. 1A-9. Experimental data during CO_2 rebreathing in one normocapnic patient.

PCO_2 (mm.Hg.)	$\dot{V}_E$ (L min^{-1})	$(dp/dt)_{max.}$ (cm. H_2O sec^{-1})
Subject. C.Why.		
62.5	12.80	17.00
69.6	13.86	16.70
73.2	13.00	17.10
76.0	14.12	17.80
78.2	14.36	18.02
82.4	14.83	19.51
Subject. Al.Mit.		
60.2	7.82	11.20
65.2	7.93	11.30
70.9	8.24	12.10
78.0	9.10	13.20
82.7	9.20	13.30

Table 1A-10. Experimental data during CO_2 rebreathing in 2 hypercapnic patients.

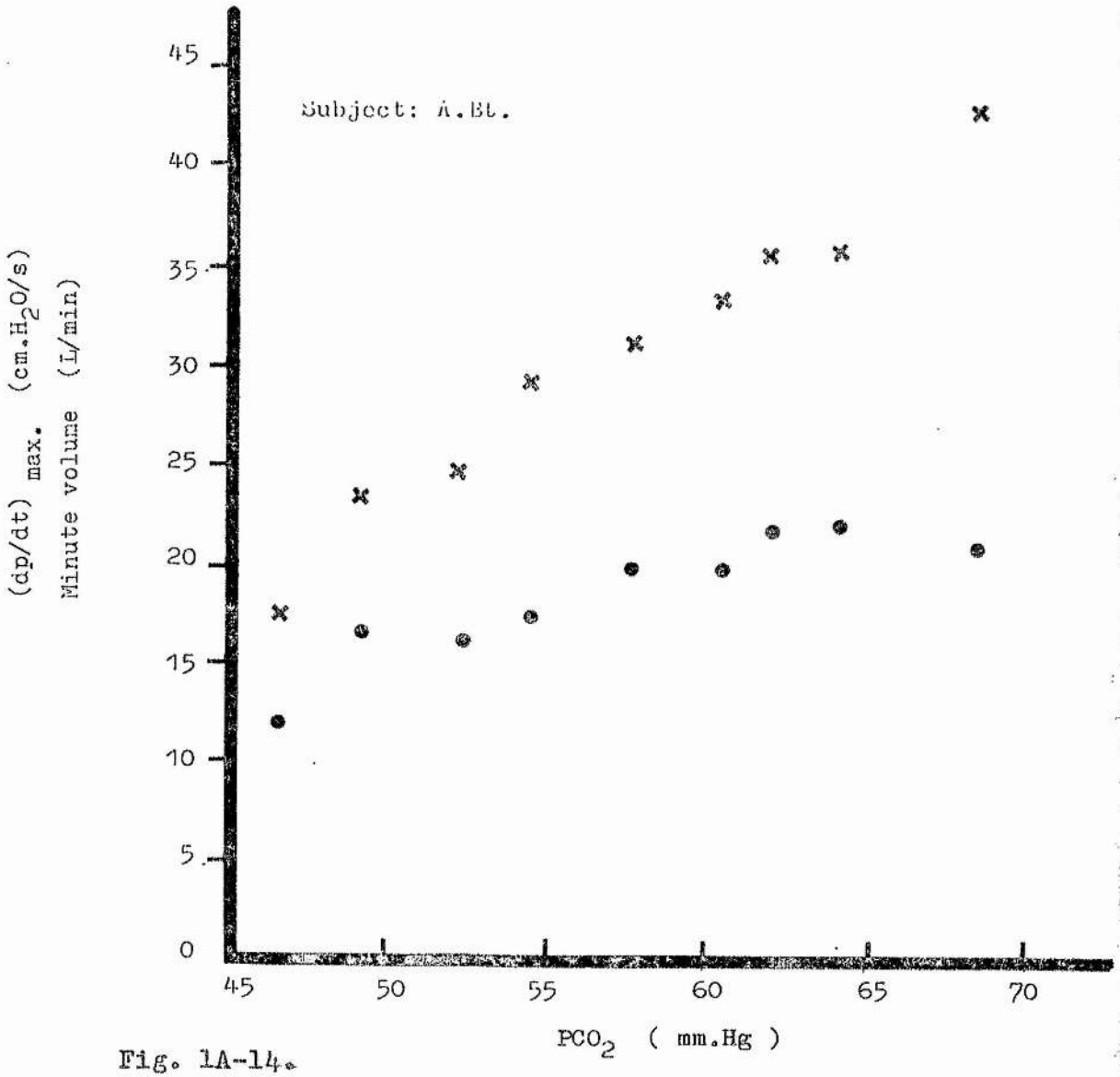


Fig. 1A-14.

Ventilatory ● and $(^{dp}/dt)_{max.}$ ✕ responses in a normocapnic patient.

FEV_1 0.9 L, FVC 2.35 L, FEV_1% 38

P_aCO_2 40.0 mm.Hg.

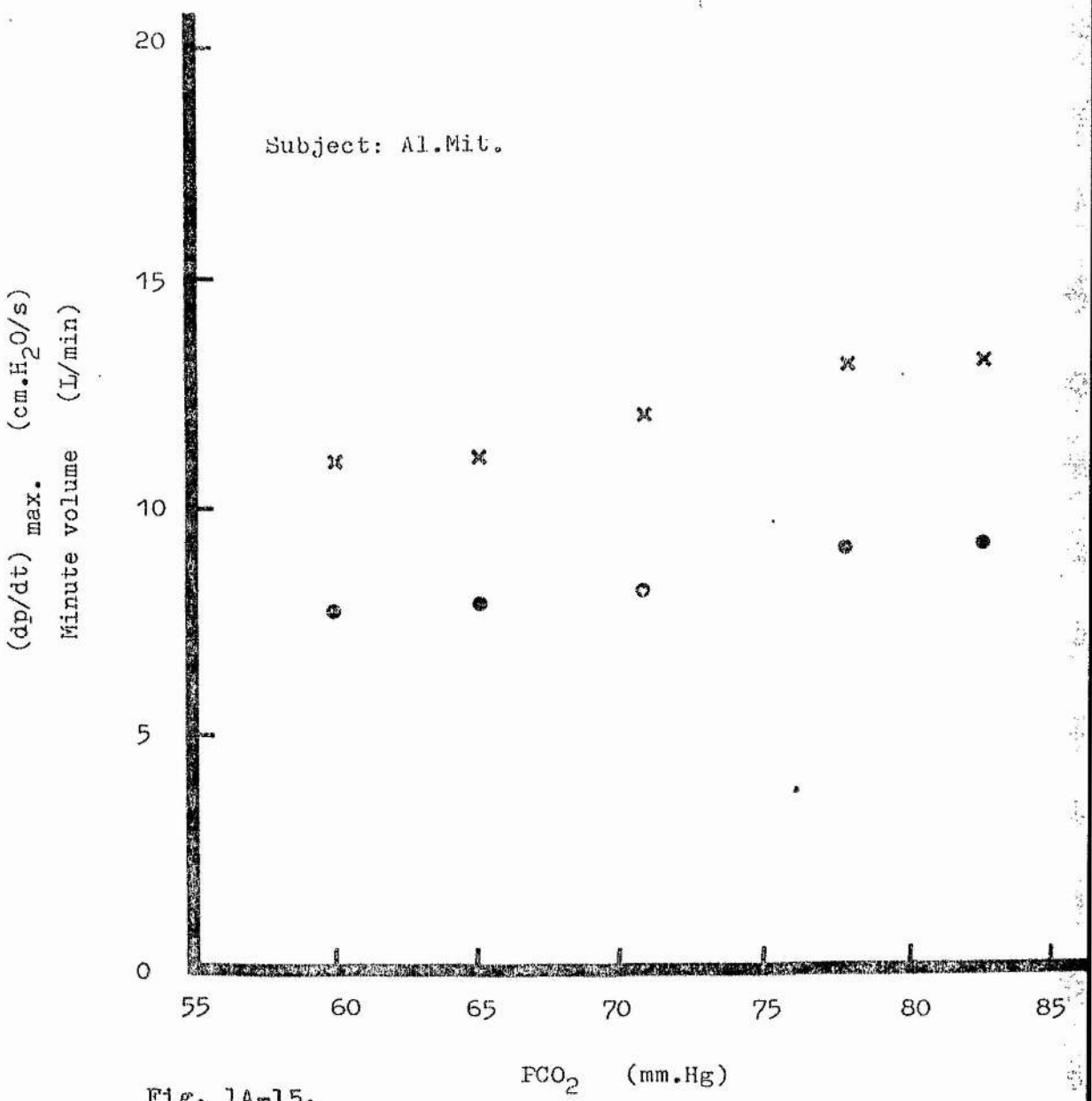


Fig. 1A-15.

Ventilatory ⊙ and $(^{dp}/dt)_{max.}$ ✕ responses in a hypercapnic patient.

FEV_1 1.1 L, FVC 1.9, FEV_1% 57

P_aCO_2 60.0 mm.Hg.

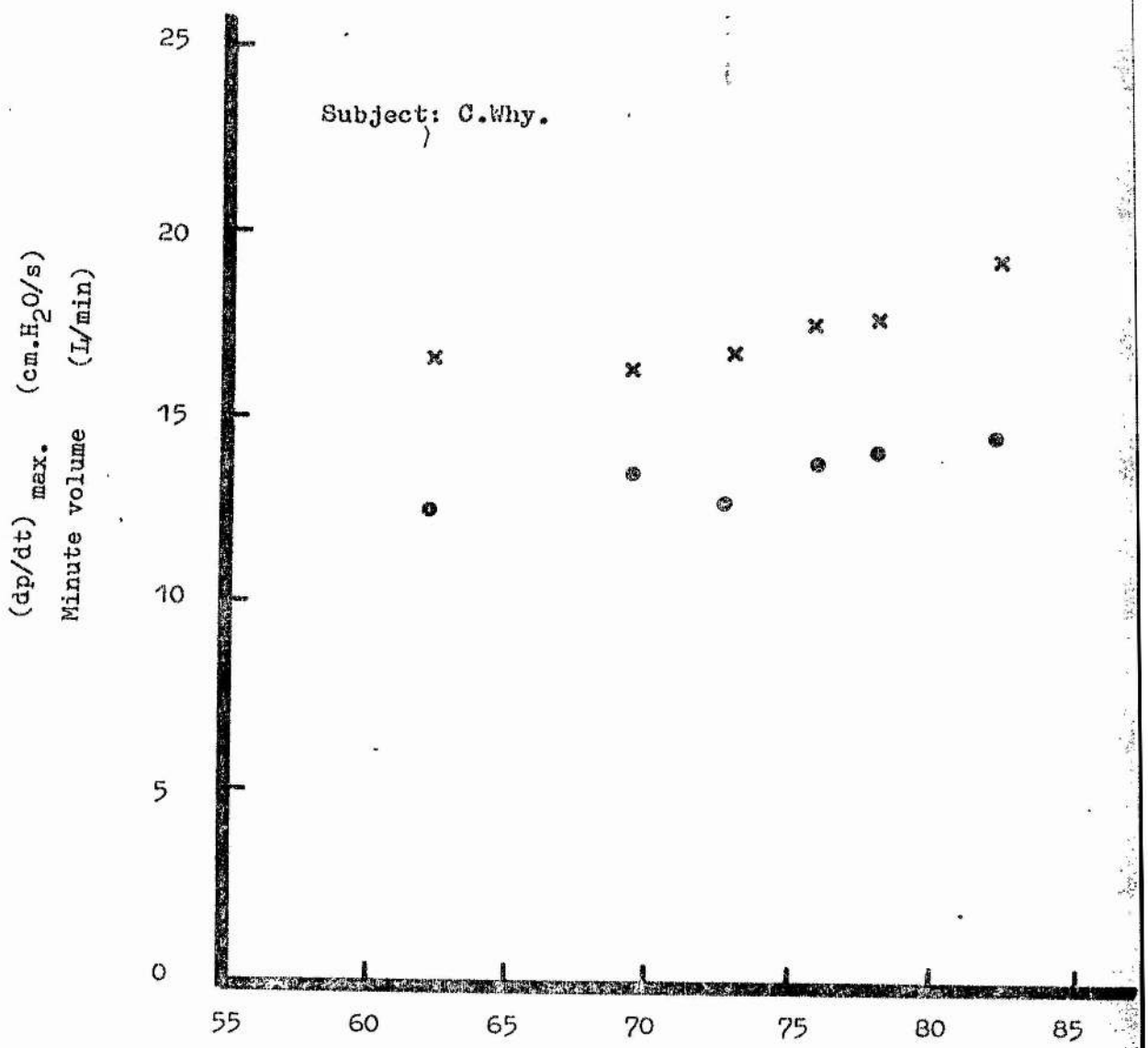


Fig. 1A-16.

Ventilatory ● and $(^{dp}/dt)_{max.}$ ✖ responses in a hypercapnic patient.

FEV_1 2.75 L, FVC 3.2 L, FEV_1% 86

P_aCO_2 61.0 mm.Hg.

(0.12 cm.H_2O sec^{-1} mm.$Hg.^{-1}$) was very low. In his case, since airways obstruction was almost non-existant this reduced CO_2 drive may be due to loss of CO_2 sensitivity due to CO_2 retention.

Correlation between airways obstruction and CO_2 response slopes.

Fig. 1A-19 shows the relationship between FEV_1% and $(dp/dt)_{max.}$ response to CO_2 in all the 49 patients studied. No significant relationship was found between FEV_1% and $(dp/dt)_{max.}$ response ($r = 0.266$. $p = < 0.05$). Similarly no significant correlation was found between FEV_1 and $(dp/dt)_{max.}$ response ($r = 0.265$ $p = < 0.05$).

Fig. 1A-20 shows the relationship between FEV_1% and ventilatory response to CO_2 in all the 49 patients . studied. A significant correlation was found between FEV_1% and ventilatory response ($r = 0.573$ $p = < 0.001$). A similar correlation was found between FEV_1 and ventilatory response ($r = 0.572$ $p = < 0.001$).

Degree of airways obstruction present.

In this study FEV_1% was taken as the index of airways obstruction. All the patients studied were chronic bronchitic patients, at different stages of severity and were undergoing treatment at time of study. Thus a whole range of FEV_1/FVC was found ranging from 30% to 86%. The mean FEV_1/FVC for hypercapnics was 48% which was slightly lower than the mean of the normocapnics with 51% but the difference was not statistically significant.

Correlation between resting $PaCO_2$ and CO_2 responses.

Fig. 1A-22 shows the significant negative relationship between $(dp/dt)_{max.}$ response and resting $PaCO_2$ levels ($r = -0.719$ $p = <0.001$).

Fig 1A-21 shows that there is slightly less correlation between ventilatory response and resting $PaCO_2$ (when compared with that between $(dp/dt)_{max.}$ response and resting $PaCO_2$) $r = -0.584$ $p = <0.001$. However, the relationship was still significant.

DISCUSSION

Patients.

Ventilatory response to CO_2

The mean ventilatory response to CO_2 in the normocapnic patients was significantly lower than that of the normal subjects. ($p = <0.001$). The hypercapnic patients showed an even more significantly lower mean ventilatory response compared to that of the normal subjects ($p = <0.001$).

Thus out of the 37 normocapnic patients studied, all except two were below the range of the normal subjects' ventilatory response. In the hypercapnic patients, all the twelve studied had a ventilatory response below the range found in the normal subjects. 12 of the normocapnic patients had a ventilatory response within the hypercapnic patients' range. Refer to Fig. 1A-17 and Table 1A-11.

From Fig. 1A-21, it can be seen that when compared to the $(dp/dt)_{max.}$ response, the ventilatory response correlated less with resting arterial CO_2 tension. There was a significant correlation between $FEV_1\%$ and ventilatory response (Fig. 1A-20) showing that ventilatory response was affected by the degree of airways obstruction present (thus the 2 normocapnic patients whose ventilatory response was within range of the normal subjects', also have $FEV_1\%$ which was similar to that found in the normal subjects).

When these 2 factors (i.e. $FEV_1\%$ and resting $PaCO_2$) are considered, it can be seen that ventilatory response to CO_2 cannot accurately measure an obstructive airways

patient's respiratory hypercapnic drive.

$(dp/dt)_{max.}$ response to CO_2

The normocapnic patients showed a lower mean $(dp/dt)_{max.}$ response than the normal subjects. However, only 5 out of the 37 normocapnic patients studied were below the range found in the normal subjects.

The $(dp/dt)_{max.}$ response in the hypercapnic patients was significantly lower than that found both for normal subjects ($p = < 0.001$) and normocapnic patients ($p = < 0.001$). Only 2 out of the 37 normocapnic patients had $(dp/dt)_{max.}$ response on the hypercapnic range. (Refer to Fig.1A-18 and Table 1A-11).

Out of the 5 normocapnic patients whose $(dp/dt)_{max.}$ response were below the range found in the normal subjects, 3 had slightly raised resting $PaCO_2$. Similarly the 2 normocapnic patients who had $(dp/dt)_{max.}$ response in the hypercapnic range also had slightly raised resting $PaCO_2$. Since the grouping of the patients into hypercapnic and normocapnic was arbitary, this may explain why their response was out with the group. Indeed the fact that these subjects with slightly raised resting $PaCO_2$ showed lower $(dp/dt)_{max.}$ response, reflects on the reliability of this measurement. They also showed a very low ventilatory response, probably reflecting a reduced CO_2 respiratory drive, although their $FEV_1/FVC\%$ was low. Matthews and Howell 1975 had a larger spread of normal subjects aged 20 to 56 years and their $(dp/dt)_{max.}$ response to CO_2 ranged from 0.6 to 4.6 $cm.H_2O\ sec^{-1} mm.Hg.CO_2^{-1}$, (mean 1.67 SE 0.09). Thus all the 37 normocapnic subjects

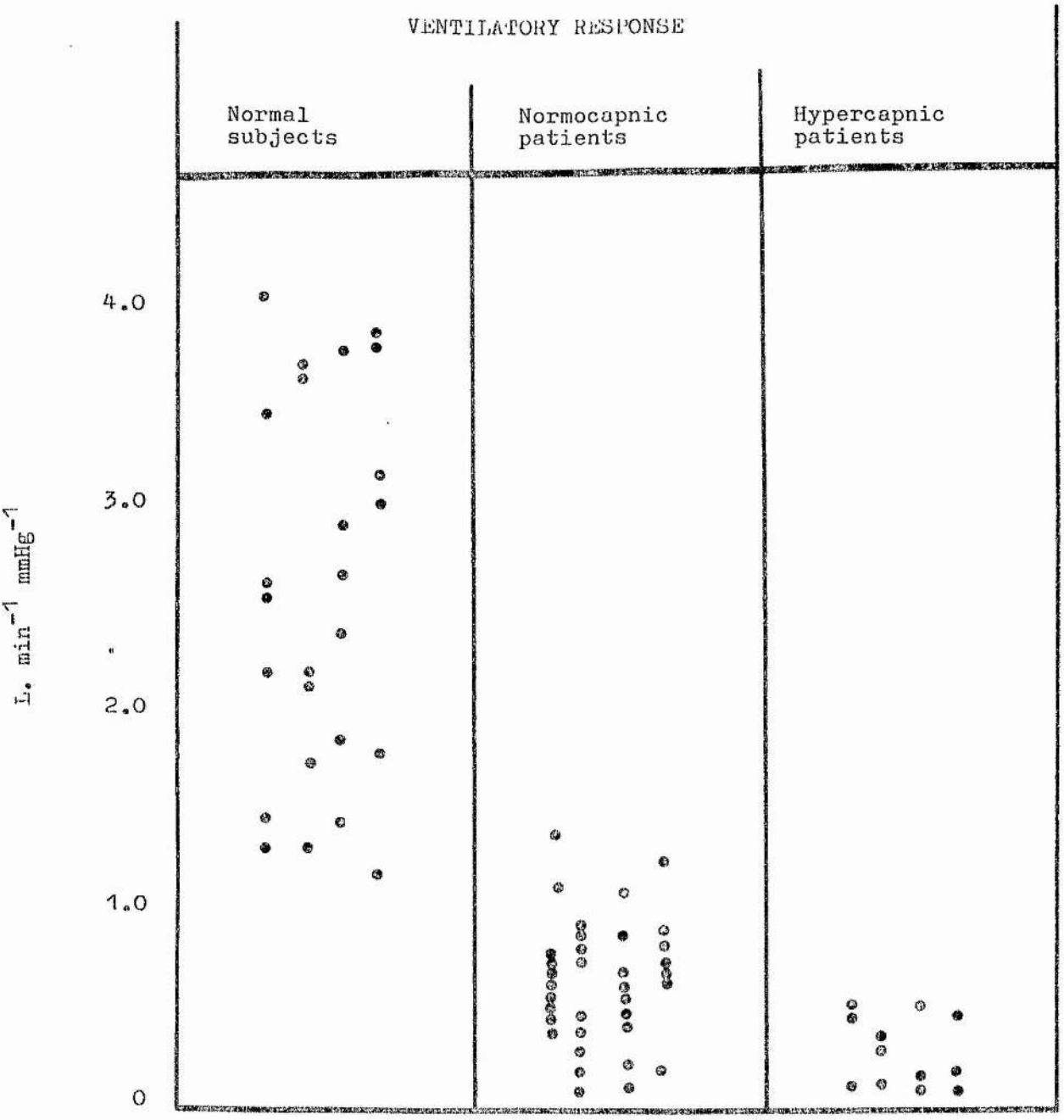


Fig. 1A-17.

Ventilatory response slopes in normocapnic and hypercapnic patients and in 25 normal subjects.

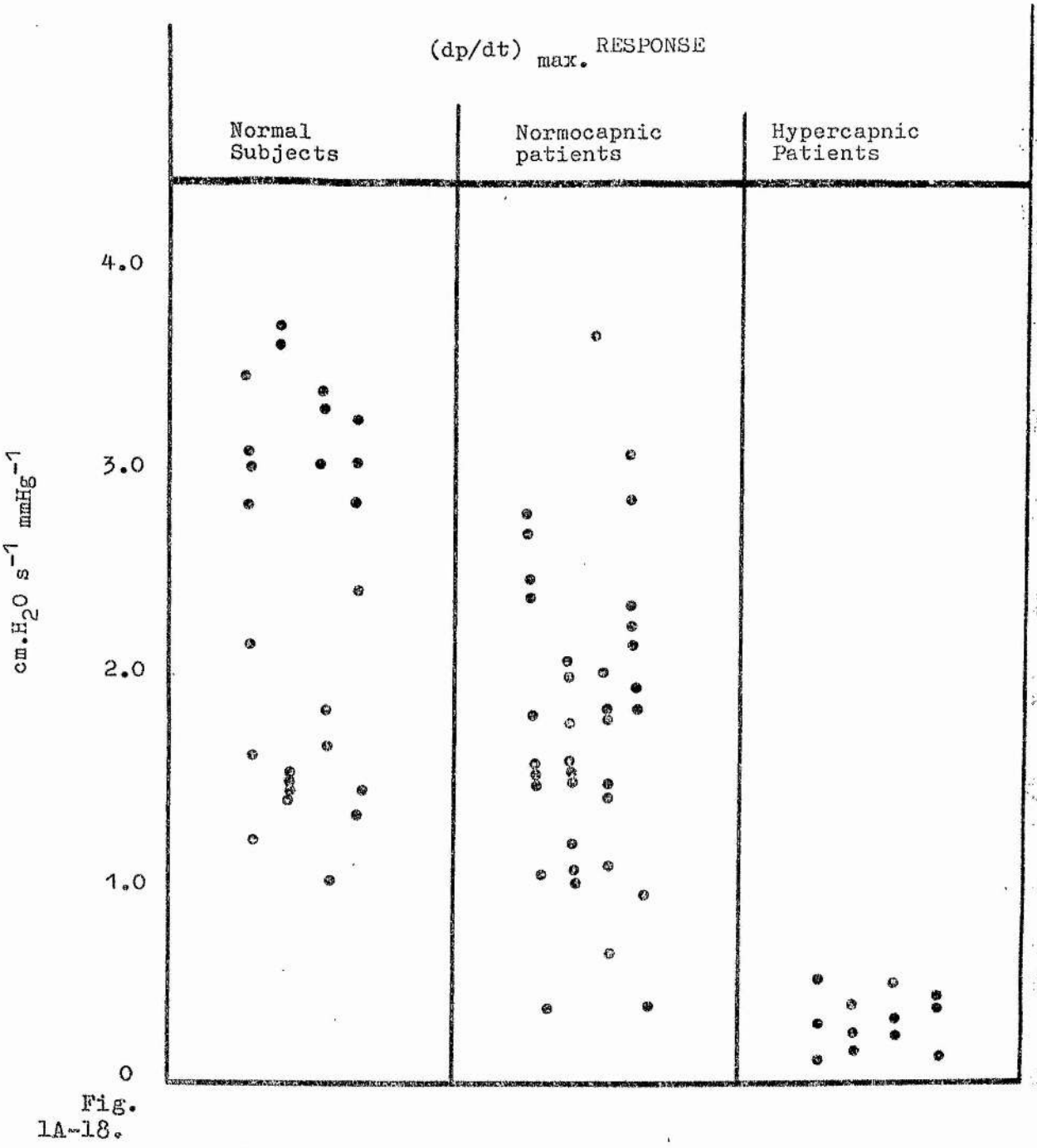


Fig. 1A-18.

$(dp/dt)_{max.}$ response slopes in normocapnic and hypercapnic patients and in 25 normal subjects.

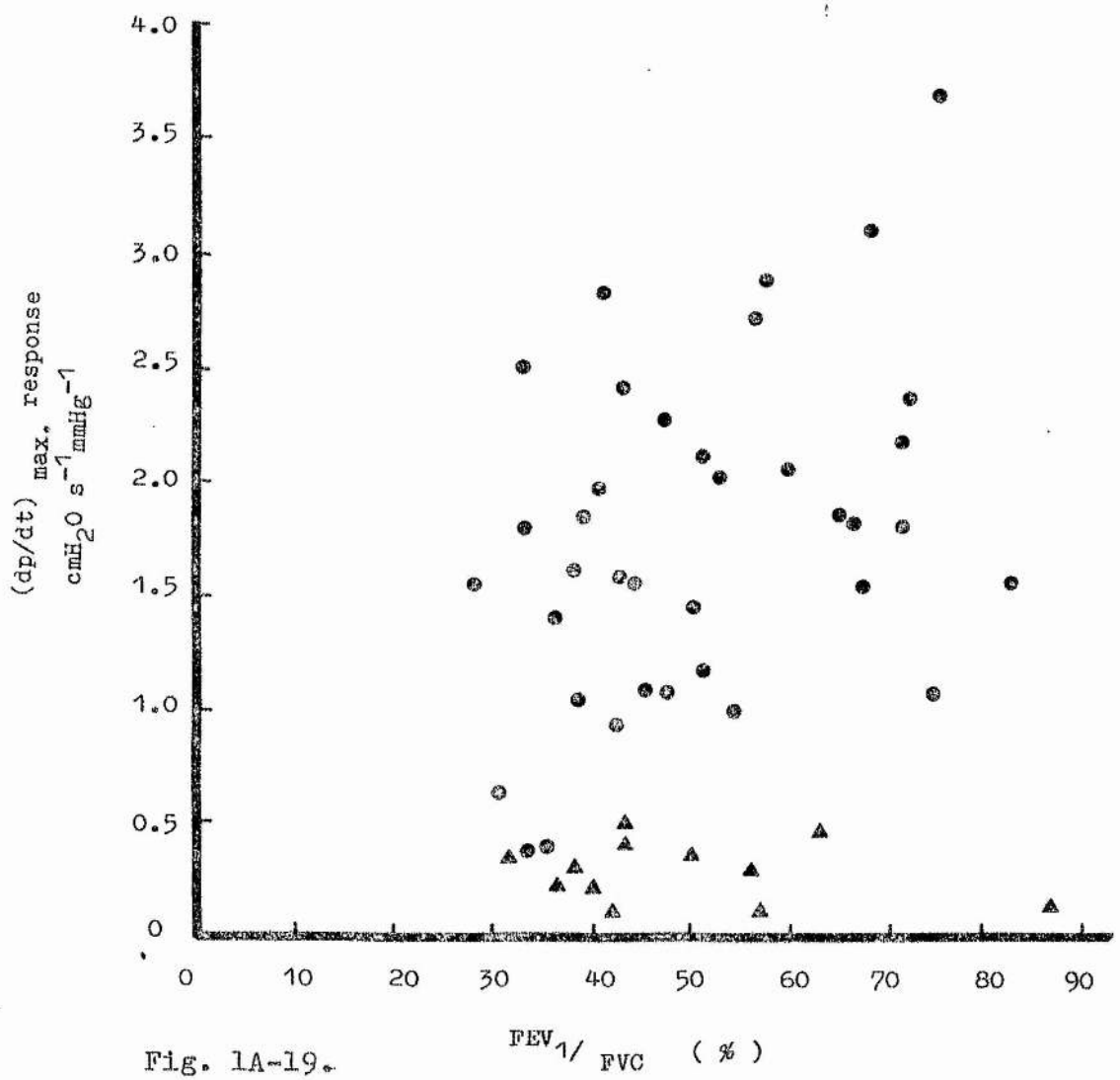


Fig. 1A-19.

Relationship between $(dp/dt)_{max.}$ response slope and FEV_1 % in 49 patients.

normocapnic, hypercapnic.

r= 0·266

p= > 0·05

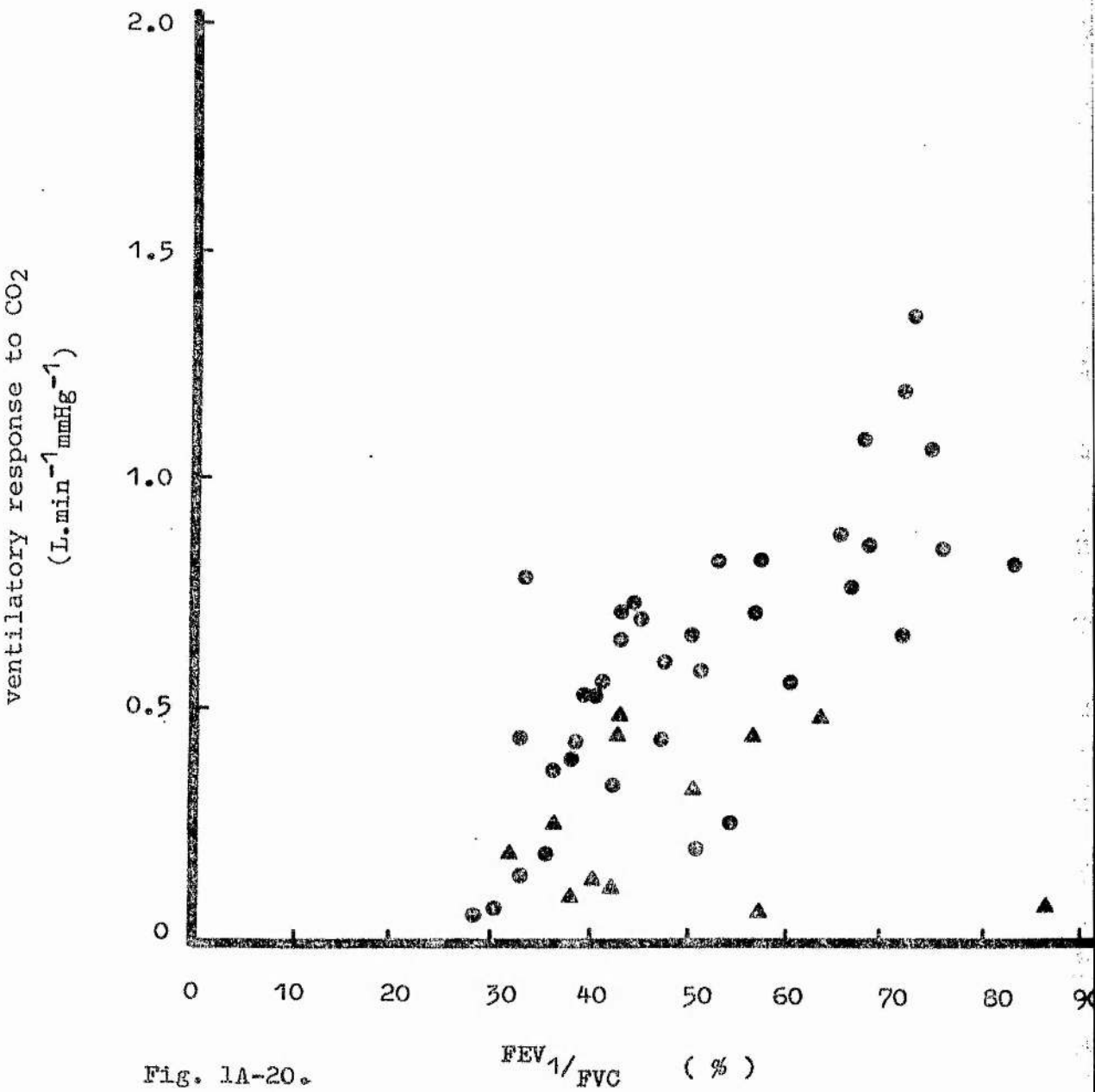


Fig. 1A-20.

Relationship between ventilatory response slope and FEV_1 % in 49 patients.

● normocapnic, ▲ hypercapnic.

r= 0·573
p= < 0·001

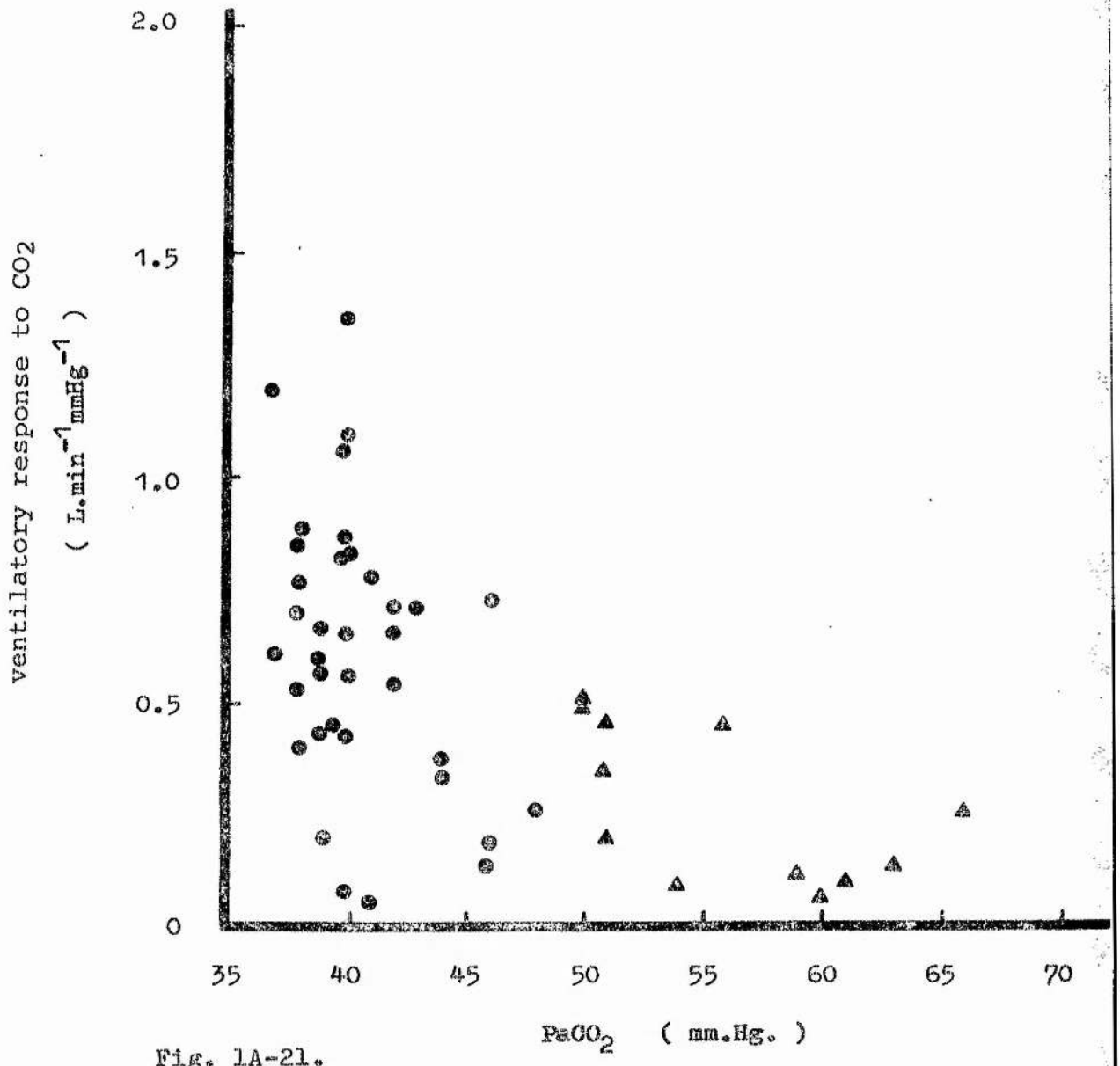


Fig. 1A-21.

Relationship between ventilatory response slope and $PaCO_2$ in 49 patients.

● normocapnic, △ hypercapnic.

r = -0.584

p = < 0.001

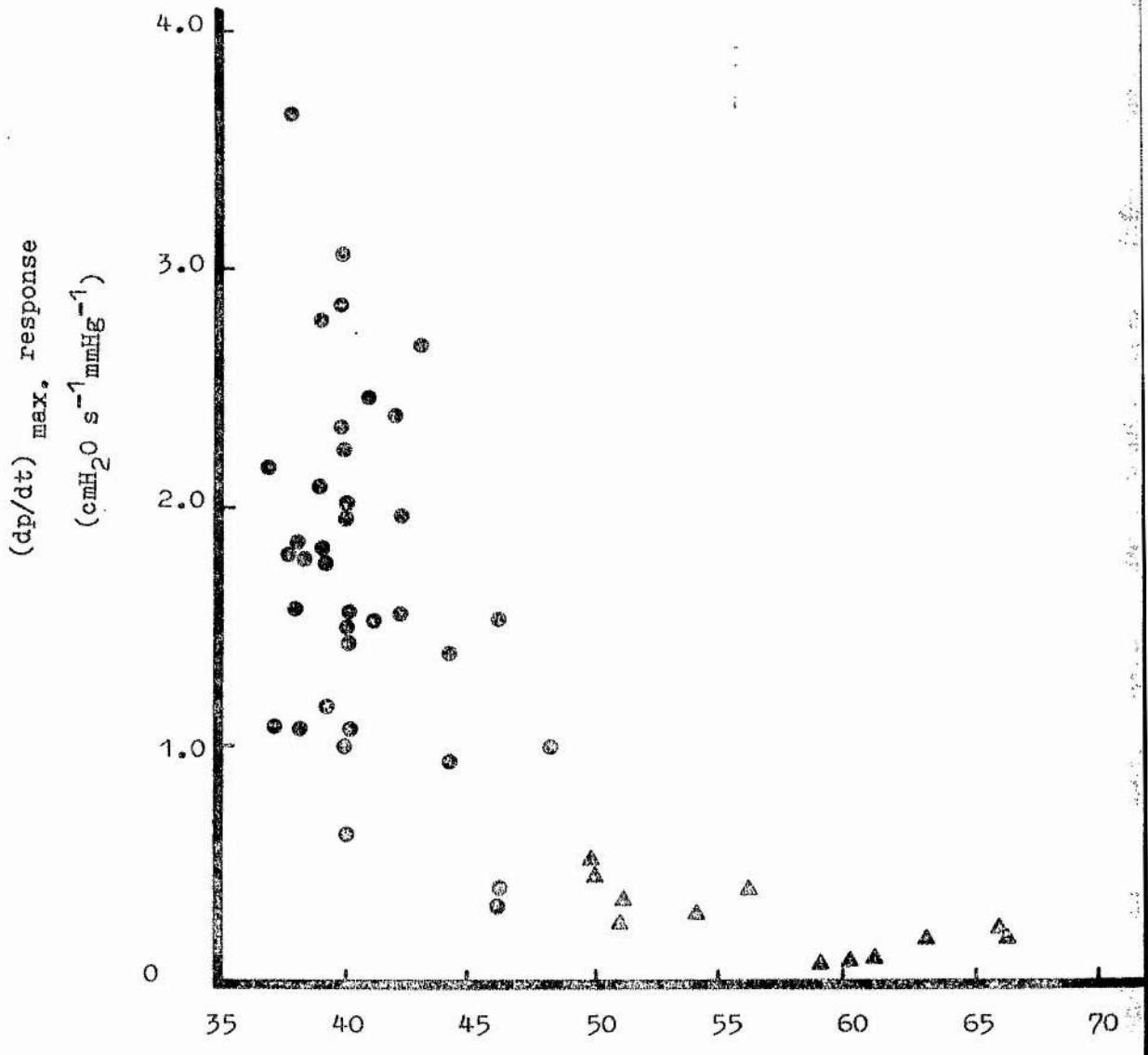


Fig. 1A-22.

Relationship between $(dp/dt)_{max.}$ response slope and $PaCO_2$ in 49 patients.

● normocapnic, ▲ hypercapnic.

r= - 0.719

p= < 0.001

Ventilatory response to CO_2 ($L.min^{-1}$ $mm.Hg.CO_2^{-1}$)

	Normal subjects.	Normocapnic patients.	Hypercapnic patients.
Mean :	2.55	0.61	0.27
SD :	0.94	0.30	0.17
SE :	0.20	0.05	0.04
range:	1.14 to 4.04	0.06 to 1.35	0.07 to 0.50

$(dp/dt)_{max.}$ response to CO_2 ($cm.H_2O$ sec^{-1} $mm.Hg.CO_2^{-1}$)

Mean :	2.38	1.56	0.28
SD :	0.90	0.67	0.14
SE :	0.18	0.13	0.04
range:	1.02 to 2.38	0.36 to 2.80	0.08 to 0.47

Table. 1A-11. Comparison of ventilatory and $(dp/dt)_{max.}$ responses in normal subjects, normocapnic and hypercapnic patients.

studied here were within the normal range of $(dp/dt)_{max.}$ in their study.

From Fig. 1A-22, it can be seen that there is a significant negative correlation between $(dp/dt)_{max.}$ and resting arterial CO_2 tension. Fig. 1A-19 shows that there is no correlation between airways obstruction and $(dp/dt)_{max.}$ response. From these observations, and a comparison with data from normal subjects, it can be seen that $(dp/dt)_{max.}$ represents a reliable measurement of respiratory drive to CO_2 which is independent of airways obstruction. Thus it is possible to monitor CO_2 responsiveness in patients along with development of airways obstruction over a long period, and to see how CO_2 retention develops.

OVERALL DISCUSSION

CO_2 rebreathing

Read 1967 developed a quick and simple method whereby ventilatory response to CO_2 can be measured. He showed that rebreathing from a small bag, containing a mixture of CO_2 (close to resting mixed venous PCO_2) in O_2, resulted in a progressive increase in PCO_2, while at the same time measurements of ventilation were made. This follows from observations made by Fowle and Campbell 1964 who found that under these conditions there is a PCO_2 equilibrium, after 15 seconds of rebreathing, between CO_2 in the mixed venous blood, arterial blood and the rebreathing bag. After the initial 15 seconds, there is a progressive increase of about 6 mm.Hg per min for the 4 minutes rebreathing. Throughout this 4 minutes, the CO_2 storage in the bag and the lungs is negligible. Read and Leigh 1967 have also shown that this rebreathing test is valid for medullary chemosensitivity assessment, thus measuring the end-tidal PCO_2 provides a reasonable index of intra-cranial CO_2 stimulus.

Use of CO_2 rebreathing in patients

The CO_2 rebreathing has been used extensively in testing CO_2 responsiveness. Jennett 1968 has shown that CO_2 rebreathing is applicable for assessment of drug effects but showed considerable variation. Jennett and Short 1973 after modifying their method studied the normal range and repeatability of response in order to compare the response of brain damaged patients. They also studied the identification of reduced peripheral chemo-reflex activity by comparison of responses to rebreathing

CO_2 in high and low O_2. They found that the response to CO_2 was greater in low O_2 tests than in high O_2 tests, and suggested that there might be peripheral chemoreflex abnormality if in repeated tests, S for low O_2 did not exceed S for high O_2. The effect of anaesthesia on CO_2 responsiveness using Read's method was studied by Derenne et al 1976 (as measured by both total mouth occlusion pressure and ventilation), to throw light on the effects of anaesthetics on the respiratory control system.

Read's method has been widely used in the study of CO_2 responsiveness in chronic bronchitics (Clark and Read 1966, Clark 1968 and Matthews and Howell 1976) to assess the overall chemosensitivity in these patients.

Comparison between Steady-State and Rebreathing methods.

The use of both steady state and rebreathing methods have been widely used for measuring ventilatory response to CO_2. Avery et al 1963 and Tenney et al 1963 in a 22-litres rebreathing circuit (in one subject), have shown that both methods gave similar results. Read 1967 confirmed that in normals, the values of S obtained by both methods are comparable. Also Clark 1968 showed that in 3 patients, with chronic airways obstruction and low Co_2 ventilatory drive, both methods give similar results.

Read and Leigh 1967 showed that both in rebreathing and steady state methods, the ratio of change in ventilation to change in PCO_2 was similar. Though the mean x intercept difference between the two methods was 8.8 mm.Hg., this difference was not significant.

The validity of Read's rebreathing method depends on the rapid attainment of a mixed venous PCO_2 plateau and thus establishing a physiologic 'open loop'. This means that there is a constant relationship established between end-tidal PCO_2 and brain tissue (Read and Leigh 1967) and this is unaffected by the level of ventilation; PCO_2 therefore rises linearly with time. It happens that ventilation under this condition also increases at nearly a constant rate. Thus a linear relationship is obtained between ventilation and end-tidal PCO_2, the slope of which, when plotted over 15, 20 or 30 second periods (Read 1967, Jennett 1968, Clark 1968 and Rebuck et al 1972) gives the response measurements.

ACUTE VENTILATORY RESPONSES

a) Acute hypoxia

It has been shown by Mitchell 1965 and Sorensen and Mines 1970 that when animals are deprived of peripheral chemoreceptors, acute hypoxia would not stimulate ventilation, but depressed it. This showed that acute hypoxic stimulation is derived from peripheral chemoreceptors.

With intact peripheral chemoreceptors, the stimulatory effects on ventilation produced by hypoxia is dependent on the sensitivity of the peripheral chemoreceptors and the sensitivity of the central chemoreceptive areas to CO_2. During acute hypoxia, ventilatory drive increases. The resulting ventilation causes hypocapnia which then decreases the ventilatory drive by the peripheral and central chemoreceptive areas. (Leusen and Demeester 1960). Thus the eventual ventilation is less than what could be expected if it were to come from peripheral stimulation only.

Thus from this it can be seen that in order to test hypoxic drive, it is important to separate the effects of CO_2 on hypoxia. There are several methods used which eliminate this CO_2 factor, resulting in an isocapnic hypoxia test. Thus an isocapnic hypoxic steady state test (Cormack et al 1957) and a rebreathing test (Godfrey et al 1971 and Rebuck et al 1973) have been used in some studies of the effect of hypoxia on ventilation.

By changing different levels of constant PO_2 during

CO_2 breathing, the interactions between ventilatory response to CO_2 and O_2 can be studied. Thus Neilsen and Smith 1952 and Lloyd et al 1958, constructed CO_2 response slopes at different O_2 concentration. It is found that with hypoxia, the CO_2 response slope became steeper implying that at any given PCO_2 increase, there was a larger ventilation increase with decreased PO_2. It also shows that for a given decrease in PO_2 the ventilation increase was greater when there is increased PCO_2. Thus it is important to note in both hypoxic and hypercapnic response test to record the PCO_2 and PO_2 state.

From the CO_2 and O_2 responses curves, Lloyd et al 1958 used a mathematical extrapolation where there is a common intercept on the zero-ventilation axis for all CO_2 response curves in an individual.

b) Acute Hypercapnia

The stimulation of ventilation by CO_2 is affected both by the peripheral and central chemoreceptive areas. The relative contribution of these areas to the total resulting ventilation is difficult to determine. Experiments on dogs and goats (Mitchell 1965 and Sorensen and Mines 1970) has shown that after denervation of the peripheral chemoreceptors, the ventilatory response to CO_2 was reduced by 20 to 45%. In the awake humans, Katsaros et al 1960 and Lambertsen et al 1961, have shown that with CO_2 breathing 25% to 40% of the ventilatory response was reduced when arterial pH was kept constant. Gray 1968 suggested that

the response to CO_2 by the carotid body was mainly a response to arterial pH, thus this magnitude of reduction is mainly due to the peripheral contribution to CO_2 ventilatory stimulation.

The sensitivity of the peripheral chemoreceptors to CO_2 depends on arterial PO_2, where lowered PO_2 increases the stimulatory effect of increased PCO_2. Thus to test the contribution of peripheral bodies to CO_2 ventilation stimulation must take into account the right PO_2 where PO_2 and PCO_2 interact as stimuli to the peripheral bodies, thus independent of their sensitivity to PO_2 changes.

Attempts have been made to separate the effects of CO_2 into two separate components, the molecular CO_2 itself or those due to the H^+, Nielsen 1936 and Gray 1946 have shown that in the V_E, $PaCO_2$ response curve, the slope of the curve shifted to the left in the presence of acidaemia (induced by NH_4Cl). Domizi et al 1959 and Saito et al 1960 showed similar results in that the V_E, PCO_2 response slopes were unchanged but displaced to the left in acidosis and to the right on alkalosis. If ventilation is plotted against pH_a instead of $PaCO_2$, the response lines are still separate (Cunningham 1974). From this it can be seen that with only arterial pH or arterial PCO_2 alone, the response cannot be predicted. The two separate stimuli are required for the prediction of the response. Since the two response slopes are parallel, stimuli proportional to $PaCO_2$ and to H^+_a act independently and additively.

Thus, from these slopes, (Cohen et al 1964 and Brown and Clancy 1965) the quantitative contributions to CO_2 response made by CO_2 and H^+ can be calculated. Lambertsen et al 1961 has shown that 45% of the response to CO_2 breathing was due to changes in blood acidity and 55% to change of blood PCO_2.

Central Chemoreceptive Areas

The presence of chemoreceptors which are anatomically separate from the carotid and aortic bodies were demonstrated by Gemmill and Reeves 1933 and Tenney and Brooks 1966, when they showed that after total denervation of the carotid and aortid bodies, CO_2 can still stimulate ventilation. Lambertsen et al 1961 showed that for an equivalent change in arterial pH, the ventilatory response is more in hypercapnia than in metabolic acidosis, suggesting that the receptors are separated from the blood stream by a diffusion barrier permeable to CO_2 but less permeable to H^+ and HCO_3^-. Hornbein and Roos 1963 and Gray 1968 also showed that these receptors respond differently from the carotid body.

The mapping of these chemosensitive areas showed that they are situated in the brain, but the exact location is unknown. The central chemoreceptive areas are stimulated, producing increased ventilation when perfused with an acid medium but depressed by an alkaline fluid. (Mitchell et al 1963 and Pappenheimer et al 1965).

Mitchell et al 1963, suggested that changes in the

composition of cerebrospinal fluid (CSF) affects the chemoreceptive areas which are sensitive to pH in their environment. They mapped out these areas on the medulla surface as being chemosensitive by applying local anaesthesia which induced apnea in anaesthesised cats. However, these chemoreceptive areas do not morphologically show any receptor cells, thus suggesting that these pH sensitive respiratory centre neurons are located superficially in these areas in the brain stem.

It has not been resolved whether the pH effect is due only to changes in extracellular pH or whether it is due to changes in intracellular pH.

The sensitivity of the central chemoreceptive areas can be expressed as ventilation response to pH changes in the brain extracellular fluid. Since the ventilatory responses are different when stimulated by pH changes induced by changing HCO_3^- and by inspired PCO_2, it is difficult to put absolute values on the sensitivity. However, maximum and minimum values were computed from data in goats by Pappenheimer et al 1965 (by Sorensen 1971). Minimum values were found by pH changes due to changing HCO_3^- and maximum values by inspired PCO_2.

In man Severinghaus et al 1963 calculated the ventilatory response to CSF pH changes during CO_2 breathing in man, assuming minimal contribution from the peripheral receptors and found that the change in ventilation per change in CSF pH was larger than that found in goats.

Different techniques for measuring CO_2 response in diseases.

From the time Scott 1920 observed that there was a reduced ventilatory response to CO_2 in patients with airways obstruction, workers have developed several methods to measure accurately this response in disease.

Cherniack and Snidal 1956 observed reduced ventilatory response to CO_2 when they introduced viscous resistance at the mouth of subjects, suggesting that this reduced response is solely due to the airways obstruction limiting the normal ventilatory flow. Similarly, Eldridge and Davis 1959 suggested that the increased resistance was responsible for the diminished ventilatory response.

Since this was so, workers tried to measure a response other than that of ventilation to assess this CO_2 drive in patients. Mechanical work of breathing as the measured response was used by Eldridge and Davis 1959 and Brodvsky et al 1960. They found that this mechanical work in normals, in normals with added external resistance, and in patients with airways obstruction all show similar slopes when plotted against arterial PCO_2. This suggested that this measurement of response would measure accurately CO_2 drive without being affected by resistance, even though the PCO_2 intercept for patients with obstruction were higher than that for normal subjects. Similarly Milic Emili and Tyler 1963 found that added viscous resistance reduced ventilatory response to CO_2 by 50%, without affecting the inspiratory work rate response.

However, when obstructive airways patients are separated into the hypercapnic and normocapnic subjects the response of ventilation to CO_2 expressed as work rate is lower in

the hypercapnics and in patients with elevated bicarbonate levels (Alexander et al 1955, Cherniack and Snidal 1956 and Park 1965).

Lane and Howell 1970 also used inspiratory work load performed during CO_2 rebreathing to assess their subjects' CO_2 drive. A significant positive correlation was found between work rate response and dyspnoes; patients with reduced response also experienced little dyspnoea despite severe airways obstruction. There was also a significant negative correlation between work rate and high resting $PaCO_2$, suggesting that a diminished work rate response would mean reduced central CO_2 sensitivity.

Similarly Fritts et al 1959 measured mechanical work as the measured response to CO_2 and found the response in 4 emphysematous patients to be normal.

O'Donnell and Hood 1971, in their study of 13 patients with obstructive lung disease and hypercapnia, used changes in intrathoracic pressure as the CO_2 drive index. This is done by measuring the end-inspiratory and end-expiratory intrathoracic pressures using an intra-oesophageal balloon during CO_2 rebreathing. They showed that with increase in P_ACO_2, the intrathoracic pressure difference increases. Patients showed a decreased CO_2 ventilatory response when compared to normals but the "pressure drive" response was the same suggesting that this "pressure drive" index is independent of airways resistance.

Another method employed is the response measured

as the oxygen cost of breathing during increased breathing. Richards et al 1958, in nine emphysematous subjects with elevated $PaCO_2$, measured the oxygen consumption for the increased ventilation and found that the response measured was similar to that of the normals. However, the ventilation attained at a given increase in oxygen consumption was much less in the patients than in the normals, suggesting that the reduced ventilatory response was due to mechanical factors.

Brodovsky et al 1960, measured oxygen consumption (as well as the mechanical efficiency) of the respiratory muscles, and likewise found no difference in CO_2 response in their patients and normal subjects. When measuring oxygen consumption as the measured response an assumption has to be made. This is the efficiency of the oxygen cost in terms of the development of mechanical work is similar during CO_2 breathing and room air in the same individual as well as when comparing different individuals.

The measurement of the integrated EMG of the diaphragm as the output from the respiratory centre was also employed to separate reduced central sensitivity from increased mechanical obstruction. Lourenco and Miranda 1968, found that the EMG activity is decreased in patients with elevated resting $PaCO_2$ when compared to that of normals and normocapnic airway obstruction patients.

Repeatability of slopes of CO_2 response using rebreathing method.

Eckenhoff et al 1956 noted that CO_2 response measure-

ments were quite repeatable. Workers have noted the variability of "normal" CO_2 response from subject to subject, without being able to identify the cause of variation. Schaefer 1958, suggested that differences in adrenal and sympathetic responses to hypercapnia might be responsible.

Jennett 1968, observed a large variability in individuals on repeated testings (in 9 subjects in 59 trials, with a mean coefficient of variation of 37% in individual subjects). However, Jennett and Short 1973, found that when 26 subjects were studied twice in an interval of 15 minutes, the average difference in slopes is of plus or minus 28%, but there is not a significant difference between the first and second tests.

Using a slight modification of Read's method, Strachova and Plum 1973, in a study of 43 subjects (normal subjects, hospitalised normals, and patients with acid-base and neurologic disorders), found more repeatable results, with an average coefficient of variation of 5.6% for each subject (for repeated tests in single day it was 5.8% and for long term repeats of a month it was 5.6%). Differences in values found in an individual subject, rarely exceeded 2 standard deviations of the mean, and they suggested that the method is reliable for assessing effect of disease on the response to CO_2.

Clark 1968, found in his study of 36 patients with chronic airways obstruction, repeatability is good with a coefficient of variation of about 10%. Within subject repeatability was better the lower the ventilatory response.

In this study ventilatory response to CO_2 repeatability was good, the mean coefficient of variation was 9% when breathing without airways resistance. With added airways resistance the mean coefficient of variation was 8%. When CO_2 response was measured in terms of $(dp/dt)_{max.}$, the mean coefficient of variation without airways resistance was 11% and with resistance was 8%. This is in agreement with the findings of Matthews and Howell 1975 who found a variation which was small and similar for ventilation and $(dp/dt)_{max.}$

Repeat tests were also carried out for the $P_{0.1}$ response to CO_2 tests. The mean coefficient of variation for both the $P_{0.1}$ and ventilatory response to CO_2 was 10%.

From this it can be seen that repeatability was similar for all three different CO_2 response measurements. Repeatability was also similar in both ventilatory and $(dp/dt)_{max.}$ response to CO_2 during resistance breathing, suggesting that both $P_{0.1}$ and $(dp/dt)_{max.}$ are reliable CO_2 response indices. In face of resistance, $(dp/dt)_{max.}$ still gives consistent values.

Possible causes of reduced hypercapnic drive in chronic bronchitic patients.

Ever since Scott 1920 observed the reduced ventilatory response to CO_2 in chronic bronchitic patients, several possible causes have been advanced to explain this observation. It is generally agreed that the loss of CO_2 responsiveness of some patients with chronic airways obstruction in the later stages of their disease is due to long exposure to CO_2. This is supported by the findings

of Shafer 1949 and Schaefer et al 1963 who showed that normal subjects, exposed to increased CO_2 concentrations for long periods, showed a decreased hypercapnic drive. However, the initial development of this loss of CO_2 response is not clear. Prime and Westlake 1954 and Park 1965 suggested that reduced responsiveness to CO_2 was the main factor responsible for CO_2 retention, whereas Lourenco and Miranda 1968 suggested that the obstruction itself was mainly responsible.

Reduction of respiratory centre sensitivity to CO_2 may be explained by several workers' findings. Vance 1966, showed that in hypercapnic and normocapnic patients there were no abnormalities in CO_2 storage. As the increase of CO_2 during rebreathing is similar for both groups, the decreased ventilatory drive in hypercapnia is probably secondary to a compensatory increment in bicarbonate content (Park 1965). He showed that increases in HCO_3^- would cause the reduced CO_2 drive slope. In hypercapnic patients the level of plasma and CSF HCO_3^- plays a role in the reduced responsiveness.

It has been shown by Fencl et al 1966 that chronic metabolic alkalosis can reduce respiratory centre responsiveness. However, the patients in this group have abnormal lung and chest wall, thus these must be considered as well. Alexander et al 1955 showed in normals that increased bicarbonate contents resulted in significant increase in $PaCO_2$. They also showed that the high bicarbonate contents in the blood does not have any

significant effect; it is the high bicarbonate contents in the spinal fluid or in the cells or in the intestinal fluid of the central nervous system which tends to minimise the effects of H^+ caused by CO_2 breathing by mass action law. Thus stimulation by less free hydrogen ions results in a decreased hypercapnic drive.

Similarly investigations by Leusen 1954, Mitchell et al 1960 and Goldring and Turino 1976, suggested that individuals with elevated extracellular HCO_3^- (thus elevated $PaCO_2$) can have reduced neural drive to CO_2 which is the result of reduced hydrogen ion generation as PCO_2 increases, this being a reversible state. It has also been reported that in chronic respiratory acidosis, the bicarbonate concentrations in the plasma and in the cerebrospinal fluid are both increased. (Cherniack and Snidal 1956, Loeschke and Mitchell 1963, Leusen 1963, Park 1965). This increase in HCO_3^- in the CSF and plasma may affect the central control of respiration in chronic respiratory acidosis.

The alternative view for the reduction of CO_2 responsiveness was that obstruction was the primary cause (Zechman et al 1957, Cherniack and Snidal 1956 and Fritts et al 1957). Cherniack and Snidal 1956, have shown that in normals, the addition of an external airways resistance reduced ventilatory response to CO_2 to that found in chronic bronchitics. The main criticism here is the fact that the ventilation being measured might by itself cause the reduction in the bronchitic patients. However, Lourenco and Miranda 1968, using EMG diaphragmatic activity suggested that the obstruction and mechanical wall abnormality would be the initial cause of CO_2 retention.

The reduction of the nervous output from the respiratory centre as a cause for CO_2 retention has been suggested by Shafer 1958 and Lambertsen 1960, who found different CO_2 sensitiveness amongst normals. Under normal conditions the respiratory centre is able to produce adequate amounts of nervous output, however in the case of respiratory loading such as in obesity or as in airways obstruction in bronchitis, the nervous outputs are insufficient. However, findings by Lourenco and Miranda 1968 do not support this hypothesis of CO_2 retention. Their patients with moderate mechanical abnormalities did not have any increased $PaCO_2$ nor decreased CO_2 drive.

Riley 1954 suggested that there are inhibitory reflexes from the chest wall or lungs due to increased work of breathing. However, experiments in dogs (Lourenco et al 1966) and in man, (Lourenco et al 1965) showed that despite excessive breathing, there was no significant effect of inhibitory reflexes. Furthermore Lourenco and Miranda 1968 showed that patients with marked mechanical alterations gave a normal or even increased diaphragmatic response to CO_2.

Guz et al 1966 on observations made on a single unanaesthetised human subject showed that ventilatory response to CO_2 (in mixture of 7% CO_2 and 93% O_2) was reduced after local anaesthetic block of the vagus and glossopharyngeal nerves in the neck. Since animal experiments have shown that inhalation of a high concentration of oxygen suppresses the sensitivity of peripheral chemoreceptors to hypercapnia, this suggests that vagal

impulses from the lungs are important in CO_2 sensitivity maintenance. Lung damage, as a result of severe airways obstruction may affect vagal discharge, thus changing CO_2 sensitivity.

Reversibility of CO_2 sensitiveness.

Fishman et al 1955 found that hypoxaemia and hypercapnia of long duration would result in irreversible alterations of respiratory centre sensitivity. However, Turino and Goldring 1976 suggested that reduced CO_2 respiratory drive due to elevated extracellular HCO_3^- can be reversed.

Theory proposed by Lourenco and Miranda 1968.

Patients with chronic airways obstruction have varying degrees of mechanical alterations of lung and chest wall, due to airways obstruction and hyperinflation. This would result in increased stimulation of the respiratory centre by afferent nerve impulses from the lungs (Lourenco et al 1966), as shown by increased diaphragmatic activity during CO_2 breathing in patients with normal blood PCO_2. When resistance is much greater, there comes a point where the respiratory centre cannot cope with increased input to provide adequate ventilation, thus CO_2 retention occurs. The degree of obstruction will thus determine CO_2 retention in chronic obstructive lung disease. It is only when CO_2 retention becomes marked that responsiveness to CO_2 becomes reduced, due to increased bicarbonate concentrations.

Park's theory.

Park 1965 suggested that mechanical factors play an

important part only in initiating CO_2 retention in chronic obstructive pulmonary disease. Reduced CO_2 responsiveness is responsible for further enhancement of CO_2 retention, in which plasma and CSF HCO_3^- plays an important role.

In some patients with acute CO_2 retention, it was found that elevation in PCO_2 if promptly restored to normal by increase in alveolar ventilation, may cause little elevation in buffer base (Cohn et al 1954). In this situation, CO_2 retention is mainly due to mechanical obstruction and PCO_2 returns to normal when obstruction improved. When CO_2 retention is sustained, plasma and CSF HCO_3^- are raised, thus changing central CO_2 responsiveness, resulting in further PCO_2 increase, thus further CO_2 retention. In this case improvement of $PaCO_2$ not only depends on improvement of mechanical factors but also on the recovery of the central responsiveness to CO_2 which takes considerable time for excretion of bicarbonate ion.

Development of total mouth occlusion pressure and $(dp/dt)_{max}$ responses to CO_2.

A new approach to measurement of the respiratory centre output is the total mouth occlusion pressure response generated against an occluded inspiratory airways. This started when Lynne-Davies et al 1971 found that in anaesthetised cats, when the airway is occluded, the inspiratory pressure developed rises progressively with increases in PCO_2. This suggested that this inspiratory

pressure developed when there is occluded airways or "mouth occlusion" could be a measurement of respiratory centre output. Similarly Grunstein et al 1973, occluded the airways of anaesthetised cats and measured the pressure wave generated during inspiration at FRC. They found that since there was no elastic recoil at relaxed FRC the pressure measured was the net pressure developed by the respiratory muscles. Since this pressure is developed against an occluded airways and there is no air flow, the measurement would be independent of airways resistance.

Following these findings, Whitlaw et al 1975 suggested that the pressure generated at the mouth at occlusion (at FRC) can therefore be used as the respiratory centre output. However, this suggestion is based on two assumptions. The first assumption is that during this period of airways occlusion, the lungs and respiratory muscles remain nearly motionless, so that the factors which transform motor-neurone discharge into pressure remain constant. Eldridge 1975 and Lourenco et al 1966, supported this assumption when they found that the integrated diaphragm EMG is linearly related to the occlusion pressure in anaesthetised animals. The second assumption made is that, the occlusion itself must not change the respiratory motorneurone discharge. Altose et al 1975 have shown that, in anaesthetised dogs, occlusion did not change the mean rate of increase of diaphragmatic EMG activity, thus supporting the second assumption.

Whitlaw et al 1975, measured the mouth pressure at

0.1 sec. after inspiration against an occluded airways ($P_{0.1}$) with rising PCO_2 in a rebreathing circuit. They found that when $P_{0.1}$ is plotted against PCO_2, the response obtained was curvilinear, with $P_{0.1}$ increasing more at higher levels of PCO_2. They also found it to be independent of pulmonary mechanics, and concluded that $P_{0.1}$ represents a useful index of output from the respiratory centre.

Maranetra and Pain 1974, in a study of normal subjects and patients with chronic airways obstruction, measured the inspiratory occlusion pressure change as an index of respiratory drive in a CO_2 rebreathing circuit. They found that there was no significant difference in this response ($\Delta P/\Delta PCO_2$), between the normals and the patients, in spite of reduced ventilatory response to CO_2 in the patients. Hypercapnic patients (mean of 51 mm.Hg.PCO_2) with airways obstruction, showed a significantly lower $\Delta P/\Delta PCO_2$ than normocapnic (mean of 40 mm.Hg.PCO_2) patients. Since there might be cortical inhibition which could influence the pressure generated against the occluded tap during inspiration, they measured the rate of change of pressure (dp/dt) with rising PCO_2. It was found that this index of CO_2 response, $(dp/dt)/\Delta PCO_2$ was significantly correlated with the total occlusion pressure response to CO_2.

Total mouth occlusion pressure has also been investigated by Altose et al 1973. They used diaphragmatic

EMG (Ep) and pressure generated by isometric contraction of inspiratory muscles as indices of CO_2 response in anaesthetised dogs and conscious man. The mouth pressure at total occlusion (Pm) was used as a measure of isometric contraction. In dogs, increase in PCO_2 results in increase in both diaphragmatic EMG and Pm; when resistance was added absolute values of EMG activity and Pm increases but the slopes of $\Delta Pm/\Delta PCO_2$ and EMG remains constant. In the 15 normals studied, the ventilation response to CO_2 correlated well with the Pm response. However, in the chronic obstructive lung disease patients, $\Delta \dot{V}_E/\Delta PCO_2$ was depressed whilst $\Delta Pm/\Delta PCO_2$ was normal, suggesting that total mouth occlusion pressure and diaphragm EMG activity can accurately assess CO_2 sensitivity even in the presence of obstruction. Lourenco et al 1966 also found that occlusion mouth pressure correlated well with phrenic nerve activity. Further Evanich and Lourenco 1974, and Evanich et al 1976 studied phrenic nerve activity compared to changes in intratracheal and intrapleural pressure during unobstructed and during tracheal occlusion in cats undergoing CO_2 rebreathing and room air breathing. They found that during both room air and CO_2 breathing the intratracheal occlusion pressure when plotted as a function of phrenic nerve activity gave a linear relationship. This suggested that intratracheal occlusion pressure could be used as a measurement of phrenic motor nerve activity.

Further Altose et al 1976 measured the unoccluded and occluded tracheal pressure in anaesthetised dogs during CO_2

rebreathing. They found that both unoccluded and occluded tracheal pressure increases with increase in PCO_2. The addition of an inspiratory flow resistance reduced ventilatory response to CO_2 but did not change the occluded tracheal pressure. This suggested that occluded tracheal pressure was a measure of respiratory efferent neural activity and could be used as an index of CO_2 drive even when increased airways resistance was present in anaesthetised animals. Similarly Isaza et al 1975, measured the occluded mouth pressure at 100 ms after occlusion (P_{100}) and peak mouth occlusion pressure (P_{peak}) in anaesthetised goats undergoing CO_2 rebreathing. When an inspiratory resistance was added, P_{100} and P_{peak} were unchanged when compared with values obtained without resistance, again showing that in anaesthetised animals, measurement of $P_{0.1}$ response as an index of CO_2 drive was independent of airways resistance.

Altose et al 1976 studied the effects of hypercapnia on mouth pressure in conscious normal man. They measured mouth pressure during complete airways occlusion at different time intervals 100, 200 and 300 ms after occlusion (P_{100}, P_{200} and P_{300}), as well as peak end-inspiratory mouth pressure (P_{peak}). P_{peak} and P_{100} increase linearly with diaphragm electrical activity and changes in P_{peak} and P_{100} correlated well with ventilatory response to CO_2, suggesting that these mouth pressure measurements give reliable indices of respiratory activity. When an external flow-resistive loading, which failed to depress$\Delta V_E/\Delta PCO_2$,

was added with hypercapnia, there was an increase in total mouth occlusion pressure. However, changes in P_{100} and P_{peak} with hypercapnia in most subjects were not affected by resistance breathing.

Lopata et al 1977, in a study of 7 normals, measured mouth pressure at 150 ms after inspiratory occlusion ($P_{0.15}$) during CO_2 rebreathing. The subjects underwent rebreathing under control conditions with the addition of 3 different types of resistive loads, namely inspiratory, expiratory and combined inspiratory-expiratory resistances. They found that there was a reduction in ventilatory response to CO_2 in all the 3 resistive loads. However, $P_{0.15}$ increases with inspriatory and inspiratory-expiratory loading but decreased with expiratory . They suggested that mouth occlusion pressure reflects the overall inspiratory neuromuscular output of the respiratory system during CO_2 rebreathing, even in the presence of resistance.

Kryger et al 1975, found that added inspiratory resistance resulted in increased $P_{0.1}$ response to CO_2 in normal subjects. Anthonisen 1976, showed that there was a higher $P_{0.1}$ response to CO_2 in asthmatics compared to normals and chronic bronchitics. Although the chronic bronchitics did show a higher $P_{0.1}$ response when compared with normal subjects, it was suggested that gradual or chronic resistive loading does not increase respiratory drive.

The rate of rise of inspiratory muscle activity at beginning of inspiration is independent of vagal activity.

Vagatomy causes increase in tidal volume, but does not change the profile of tidal volume tracing, only by prolonging inspiration. Thus dp/dt or rate of rise of inspiratory muscle activity is independent of vagal influence.

Measurement of total occlusion pressure in conscious man is quite difficult, as awareness would cause exaggerated readings especially towards the later part of inspiration (i.e. at peak measurements). As reaction time in subjects studied by Whitlaw et al 1975 was never shorter than 0.15 sec., mouth occlusion pressure at 0.1 sec., was used as the respiratory index, in order to be free of reflex action. Matthews and Howell 1974, also measured the pressure at the mouth when airways are transiently occluded during CO_2 rebreathing. This is achieved by using a two-way Douglas valve which has an opening pressure of about 1cm. H_2O. The resulting pressure wave recorded is then differentiated electronically and the maximum rate of change of pressure recorded as $(dp/dt)_{max.}$. In normals the $(dp/dt)_{max.}$ response correlated well with ventilatory change during CO_2 rebreathing. When external resistance was added ventilatory response to CO_2 was reduced, the $(dp/dt)_{max.}$ response remained relatively unchanged, suggesting it as a measurement of CO_2 drive unaffected by resistance.

Matthews and Howell 1975, in a study of chronic bronchitics, found that while the ventilatory response to CO_2 was reduced, the $(dp/dt)_{max.}$ response was normal in normocapnic but diminished in hypercapnic patients.

Stanley 1977 studied both total mouth occlusion pressure and $(dp/dt)_{max.}$ during progressive hypercapnia in 12 normal subjects. He found that both $P_{0.1}$ and $(dp/dt)_{max.}$ were linearly related to PCO_2 and also that their changes in hypercapnia were closely correlated with ventilatory response. He suggested that $(dp/dt)_{max.}$ could be used as an easily measured alternative to $P_{0.1}$ for the respiratory response to hypercapnia.

Effect of a change in Functional Residual Capacity.

The measurement of $P_{0.1}$ and $(dp/dt)_{max.}$ as indices of respiratory drive depend on the FRC remaining relatively constant throughout their measurement (Whitlaw et al 1975) Though no direct measurements of lung volumes were made in this study, circumstantial evidence is presented below to discuss the effects of changes of FRC on the $(dp/dt)_{max.}$ and $P_{0.1}$ responses. Changes in FRC, by changing the length and geometry of the inspiratory muscles change the amount of pressure generated in response to a fixed neural output. Evanich et al 1973 have shown that for a given level of electrical stimulation, the pressure generated by the respiratory skeletal muscles, varied with their length and hence would depend upon FRC.

Marshall 1962, Sant 'Ambrogio 1970 and Minh et al 1976 have shown that when lung volume increases, the efficiency of the inspiratory muscles may decrease. Woldring 1965 and Stanley et al 1975 also showed that, in animals, there was a reduction in diaphragmatic activity in response to CO_2 when lung volume was increased.

Edstrom et al 1976 suggested that the reduction in ventilatory response to CO_2 when measured during restrictive loading breathing in normals can be due to an increase in the end-expiratory level. They further suggested that reduced ventilatory response seen clinically can be attributed mainly to this increase in end-expiratory level.

Flenley et al 1971 showed that in conscious man, an increase in lung volume, produced by raising mouth pressure to 30 cmH_2O, reduced the tidal volume response to CO_2 but the corresponding increase in respiratory rate restored the total ventilatory response.

Marantera and Pain 1974, found that changes in FRC did not change mouth occlusion pressure response to CO_2 provided airways occlusion occurred within 200 ml. of start of inspiration (approximately equivalent to 200 msecs).

Fitzgerald et al 1976 found significant increase in FRC in awake, seated subjects during both hypercapnia and hypoxia tests.

Kelsen et al 1976 and Cherniack et al 1976, have shown that during normal breathing, the FRC is not usually changed by added respiratory resistance. Rigg et al 1974 have shown that the ventilatory response to CO_2 in normal subjects did not show any significant change on changing from a lying to a sitting position. Both the $\Delta\dot{V}E/\Delta PCO_2$ slope and the level of the slope did not change. Since FRC may fall substantially in the supine position, it can be suggested from this that ventilatory response to CO_2 may not be affected by changes in FRC within the range studied. Similarly Cherniack et al 1976, also showed that the

ventilatory response to CO_2 was unaffected by changes in body position (sitting and supine). Thus the use of $P_{0.1}$ in this study as a respiratory drive index during unrestricted CO_2 rebreathing seems to be reliable.

Kryger et al 1975 have shown no change in the FRC of his subjects during both CO_2 breathing and hypoxia, with and without inspiratory resistance. Grassino et al 1973 and Pengelly et al 1971 found only small and inconsistent changes in FRC with CO_2 breathing. Studies by Cunningham 1974 has shown that hypoxia itself has no effect on FRC.

Matthews and Howell 1974 in a study of 32 normals and 6 patients recovering from bronchial asthma found that during CO_2 rebreathing, there was no constant changes in FRC. When lung volume increases, there will be flattening of the diaphragm. This will result in shortening of the muscle fibres, reduced mechanical advantage of the respiratory muscle, and thus a diminished force of contraction. This will be reflected in reduced absolute levels of $(dp/dt)_{max.}$ However, if the speed of contraction increases along with this reduced force of contraction, as the findings of Flenley et al 1971 suggested, then there would not be any change in the absolute values of $(dp/dt)_{max.}$. As shown by Altose et al 1976, even if there was a change in absolute values of $(dp/dt)_{max.}$, during CO_2 rebreathing with airways restriction, the slope of $(dp/dt)_{max.}$ response to CO_2 will still be unchanged in the same subject. Furthermore, Matthews and Howell 1974 found that when lung volume was increased the $(dp/dt)_{max.}$ response slopes were not reduced. Also the normals in

their study could voluntarily generate a higher $(dp/dt)_{max.}$ at lung volumes approaching total lung capacity, showing again that the $(dp/dt)_{max.}$ response slope is unlikely to be reduced by lung volume increases.

In this present study no lung volume measurements were made. However, the circumstantial evidence presented above would show $(dp/dt)_{max.}$ to be a reliable index of respiratory drive for both hypercapnic and hypoxia studies should there by any changes in FRC. The presence of artificially added resistance in normals and obstructive airways patients would still not affect $(dp/dt)_{max.}$ response even if FRC changes were present.

The effect of resistance on $P_{0.1}$ and $(dp/dt)_{max.}$ response to CO_2.

In this study, none of the 25 normals studied showed any significant change in the CO_2 response, in the presence of added resistance when measured in terms of $(dp/dt)_{max.}$ response. This demonstrated that $(dp/dt)_{max.}$ response to CO_2 was not affected by airways resistance, thus making it a reliable index of respiratory centre output in normals as well as patients with airways resistance.

Marantera and Pain 1975 measured the $P_{0.1}$ response to CO_2 in normals and patients with airways obstruction. They found that whilst the ventilatory response to CO_2 was significantly reduced in patients when compared with normals the $P_{0.1}$ response to CO_2 of the patients was not significantly different from that of the normals. This suggested that $P_{0.1}$ response to CO_2 was not affected by

airways obstruction. $(dp/dt)/\Delta PCO_2$ was also calculated and was highly correlated with $\Delta P/\Delta PCO_2$.

Altose et al 1976 studied the total occlusion pressure response to hypercapnia in normals with and without added airways resistance. In all the subjects studied, the absolute values of occlusion mouth pressure was greater at all levels of PCO_2 in presence of loading. However, the changes in mouth occlusion pressure with hypercapnia in most of the subjects was unaffected with resistance breathing. They suggested that in these subjects, changes in occluded mouth pressure may be useful as an index of respiratory hypercapnic chemosensitivity even in presence of airways resistance.

Cherniack et al 1976 found that in preliminary studies in patients with chronic obstructive lung disease, there was little or no increase in $P_{0.1}$ with increased inspiratory resistance. However, the occlusion pressure response to CO_2 was similar for normals and eucapnic patients with obstructive lung disease and increased FRC.

Kryger et al 1975 found that the $P_{0.1}$ response to CO_2 increased with inspiratory resistance. Similarly Lopata et al 1977 found that inspiratory resistance as well as inspiratory-expiratory resistance increased mouth occlusion pressure response to CO_2. However, expiratory resistance alone decreased the mouth occlusion pressure response.

Zackon et al 1976 found that the $P_{0.15}$ response to CO_2 in asthmatics were higher than that of chronic bronchitics and normals. They suggested that this may be due to the effect of acute airways resistance.

From the studies above, it can be seen that there were

variable results obtained when $P_{0.1}$ response to CO_2 were measured during airways resistance. However, in this study and in those of Matthews and Howell 1975 and 1976 the $(dp/dt)_{max.}$ response was unaffected by added airways resistance and in the normocapnic chronic bronchitics, the $(dp/dt)_{max.}$ response was similar to that of the normals. This suggests the reliability of $(dp/dt)_{max.}$ response as an index of respiratory drive to CO_2 even in face of loading.

SECTION 1B

RELATIONSHIP BETWEEN $(dp/dt)_{max.}$ AND DIAPHRAGMATIC ELECTRICAL ACTIVITY IN ANAESTHETIZED RABBITS.

INTRODUCTION.

The ventilatory response to hypercapnia gives a true index of medullary centre response when the ventilatory mechanism is normal. However, with lung abnormality or airways obstruction, this measurement is misleading as it is affected by the mechanical load. As discussed before many methods have been employed to measure the CO_2 responsiveness which would be unaffected by airways obstruction.

During CO_2 breathing, the electrical activity of the respiratory muscles, could give a more direct measure of neural output than either the ventilation or the work of breathing (Lourenco et al 1966, Shannon and Zechman 1972). But when there is impairment of the chest-wall or lung movements, the electrical activity of the inspiratory muscles automatically increases (Lourenco et al 1966, Wiley and Zechman 1969, Shannon and Zechman 1972). Thus in order to measure the electrical activity of the inspiratory muscles, as a reliable index of CO_2 drive, the effects of mechanical loading has to be separated from those of hypercapnia. Thus Altose et al 1975 found in dogs that whilst the intercostal muscle activity was unreliable as CO_2 drive index when loading occurs, the diaphragmatic EMGs were unaffected by mechanical loadings during hypercapnia thus providing a reliable index of CO_2 response.

In this study, in anaesthetized rabbits, the ven-

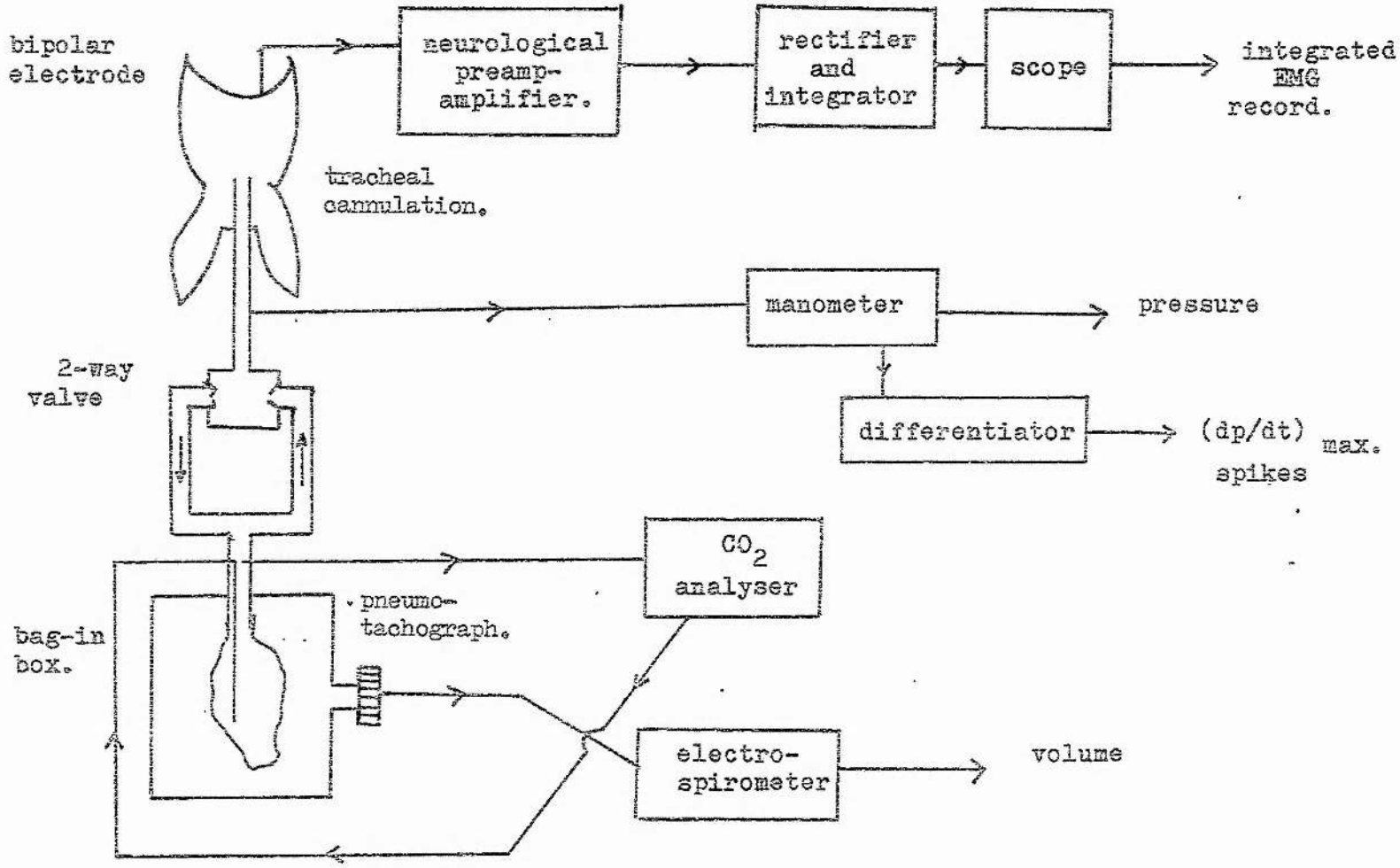


Fig IB-a Diagram to show apparatus used to record ventilatory, $(dp/dt)_{max.}$ and diapragmatic electrical activity to CO_2 in anaesthetized rabbits.

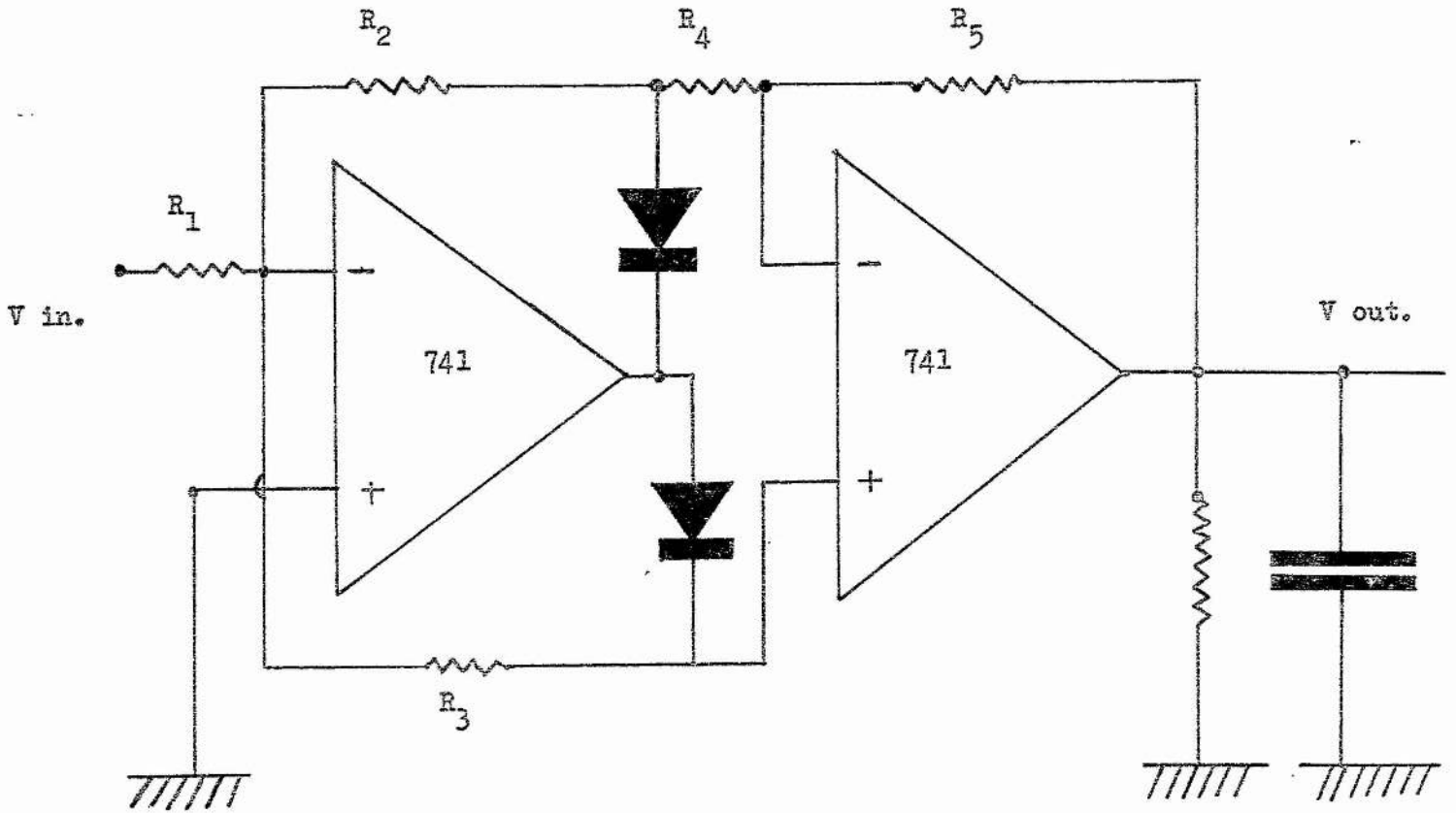


Fig. 1B-b. Circuit diagram of full wave rectifier with R-C integrator.

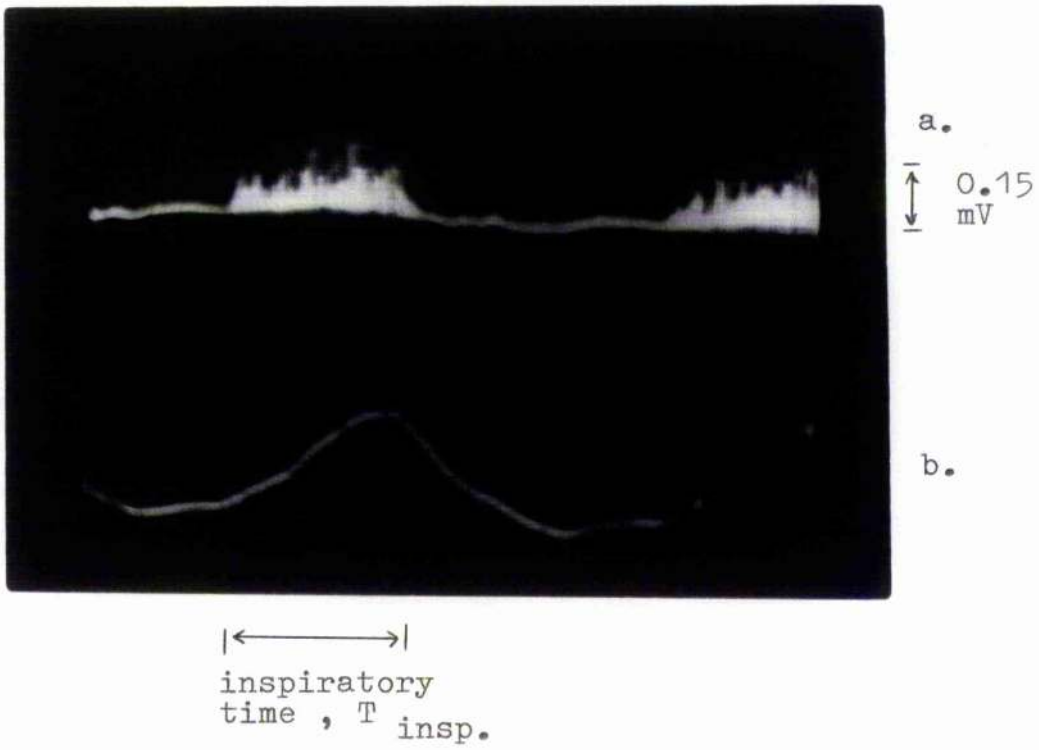


Fig. 1B-c

Tracing on scope, of rectified diaphragm EMG (channel a) and its corresponding R-C circuit integration. (channel b).

tilatory, $(dp/dt)_{max.}$ and diaphragmatic responses to CO_2 were studied during unrestricted and also restricted airways breathing. The relationship between $(dp/dt)_{max.}$ and diaphragmatic electrical activity was investigated.

Methods

7 adult rabbits were used in this study. The weight ranged from 2.5 to 3.5 kg. Anaesthesia was induced first using halothane and nitrous oxide mixture and then by urethane (1.5 gm/kg.) infused intravenously.

The set-up is as shown in diagram, Fig 1B-a. The trachea was cannulated using a large bore tube and this was connected to a rebreathing bag of 0.75 litres capacity in a box. A pneumotachograph head was attached to an outlet from the box, and connected to an electro-spirometer (Mercury) to obtain volume measurements.

A two-way Douglas-type valve was attached to the tracheal cannula. The opening pressure of the valve at 0.5 cm H_2O provided a transient inspiratory occlusion during breathing. An outlet tube between the cannula and the two-way valve was attached to a manometer to measure pressure changes. These pressure changes were recorded on a two channel fast responding pen-recorder (Brush). In one channel the pressure change was recorded whilst the other recorded the differentiated signals of the pressure changes. The differentiated signal was recorded as spikes, the height of which represented the $(dp/dt)_{max.}$ (similar to Section 1-A).

Continuous CO_2 readings were made from the re-breathing bag using an infra-red CO_2 analyser (Beckman LBI). The air sample after passing through the CO_2 analyser was pumped back into the bag.

A mid-line abdominal incision was made. A bipolar platinum electrode was then inserted into a muscular portion of the diaphragm. The electromographic potentials, recorded between 120 and 2,000 H_z were amplified by a neurological preamp-amplifier unit, then rectified and integrated using a R-C circuit (Fig.1B-'b.). The rectified and integrated EMGs were recorded on a Tektronic oscilloscope and also recorded on fast re-sponding pen-recorder.

The integrated EMG was recorded for each single inspiration (see Fig.1B-'c'). The duration of the inspiratory burst was also recorded ($T_{insp.}$). Only the EMGs coincident with the inspiratory airflow were taken in measuring the integrated EMGs and inspiratory time.

For measurements on effects of added resistance, a rubber bung with a small bore was used which produced a resistance of 200 cm.H_2O/L/sec. This level of resistance was approximately 10 times the resting total respiratory resistance in rabbits (25 to 37 cm.H_2O/L/sec. Davidson et al., 1966). The resistance was placed between the cannulation and the inspiratory valve.

All the rabbits underwent 4 tests each (3 without resistance and 1 with added airways resistance). There was an interval of 20 minutes between the tests for recovery from CO_2 rebreathing.

Treatment of data

The integrated EMG recorded was for each burst of inspiration. Five integrated recordings were taken and the average height determined for each 30 seconds period during CO_2 rebreathing. The total integrated EMG activity was compared with that of the value obtained at rest (i.e. without CO_2 rebreathing) just before the experiment started. With increase in PCO_2, the increase in total EMG was expressed as percentage increase from the rest values.

Inspiratory duration ($T_{insp.}$) was measured from the inspiratory burst of EMG activity.

The average rate of EMG activity was obtained from dividing total EMG activity by $T_{insp.}$. With increasing CO_2, the average rate of EMG activity was compared with resting value and expressed as percentage increase.

Minute volume was obtained by adding the individual tidal volume recordings.

RESULTS

(Table 1B-1 and 1B-2 shows the overall results obtained during the study).

Ventilatory response

There was a linear relationship between ventilation and end-tidal PCO_2. Increases in PCO_2 resulted in increase in ventilation.

The ventilatory response to CO_2 ranged from 48.3 to 82.3 $ml.min^{-1}mm.Hg.CO_2^{-1}$ (mean 65.8 SD 8.1 SE 1.7). This lies within range of those found by Richardson and Widdicombe 1969 in anaesthetised rabbits, mean 65 $ml.min^{-1}mm.Hg.CO_2^{-1}$. The addition of the mechanical resistive load resulted in a mean reduction of 35% in the slope of CO_2 ventilatory response. (Significant at $p = < 0.001$). (Fig. 1B-1).

$(dp/dt)_{max.}$ response.

There was a linear relationship between $(dp/dt)_{max.}$ and end-tidal PCO_2, with $(dp/dt)_{max.}$ increasing with PCO_2 increase.

The $(dp/dt)_{max.}$ response to CO_2 ranged from 0.90 to 2.90 $cm.H_2O\ s^{-1}mm.Hg.^{-1}$ (mean 1.53 SD 0.50 SE 0.10). There was no significant reduction in the response slope with the addition of the airways restriction. (Fig.1B-2).

		$\Delta VE/\Delta PCO_2$		$\Delta(dp/dt)_{max.}/\Delta PCO_2$		Δtotal EMGs/ΔPCO_2		$\Delta Ad/\Delta PCO_2$	
		No R	R	No R	R	No R	R	No R	R
	1.	71.9	53.4	1.60	1.70	4.38	4.54	7.87	7.92
Rabbit 1.	2.	68.3		1.50		4.20		10.10	
	3.	65.4		1.20		4.35		7.54	
	4.	78.9	57.5	2.90	2.70	6.45	6.30	14.90	14.80
Rabbit 2.	5.	70.3		1.85		5.90		11.65	
	6.	71.4		1.70		4.85		10.85	
	7.	66.6	42.1	1.53	1.56	4.10	4.30	9.50	9.60
Rabbit 3.	8.	65.6		1.50		3.50		6.50	
	9.	70.4		1.65		5.75		6.85	
	10.	60.7	35.4	1.20	1.40	3.50	3.40	6.60	6.40
Rabbit 4.	11.	59.4		1.10		3.25		6.35	
	12.	64.0		1.30		3.70		6.95	
	13.	48.3	30.3	0.90	0.98	3.00	3.20	6.10	5.73
Rabbit 5.	14.	55.5		1.15		3.25		6.20	
	15.	62.0		1.20		4.35		6.30	
	16.	58.3	36.7	1.50	1.30	3.60	3.50	7.10	7.30
Rabbit 6.	17.	57.3		1.05		3.90		7.34	
	18.	60.3		1.15		4.05		7.85	
	19.	82.3	49.5	2.47	2.40	8.24	8.26	16.60	15.71
Rabbit 7.	20.	74.4		2.30		7.20		14.30	
	21.	71.4		1.40		6.95		10.75	

Table 1B-1. Overall results of responses to CO_2 in 7 anaesthetised rabbits.

Table 1B-1. units used.

$\Delta \dot{V}E / \Delta PCO_2$	ventilatory response to CO_2 $ml.min^{-1} mm.Hg.^{-1}$
$\Delta (dp/dt)_{max} / \Delta PCO_2$	$(dp/dt)_{max.}$ response to CO_2. $cm.H_2O\ sec^{-1}\ mm.Hg.^{-1}$
Δtotal EMG $/ \Delta PCO_2$	total EMG response to CO_2 % increase/mm.Hg.CO_2
$\Delta Ad / \Delta PCO_2$	average rate of EMG response to CO_2. % increase/mm.Hg.CO_2

Table 1B-2. (overleaf). Overall analysis of responses to CO_2 in 7 anaesthetized rabbits.

Table IB-2.

	No resistance		Added resistance	
	7 rabbits 21 observations.	7 rabbits 7 observations.	7 rabbits. 7 observations.	
Ventilatory response	($ml.min^{-I}\ mm.Hg^{-I}$)			% change.
range	48.3 to 82.3	48.3 to 82.3	30.3 to 57.5	-42 to -26
mean	65.8	66.7	43.5	-35
SD	8.1	12.0	10.1	
SE	1.7	4.5	3.8	2

Significant reduction in slope with airways restriction. (p = 0.001)

$(dp/dt)_{max.}$ response.	($cm.H_2O\ sec^{-I} mm.Hg^{-I}$)			% change.
range	0.90 to 2.90	0.90 to 2.90	0.98 to 2.70	-13 to +16
mean	1.53	1.73	1.72	+ 1
SD	0.50	0.70	0.61	
SE	0.10	0.26	0.23	3

No significant change in slope with airways restriction.

Table 1B-2

(contd.)

	No resistance.		Added resistance.
	7 rabbits. 21 observations.	7 rabbits. 7 observations.	7 rabbits. 7 observations.
total EMG response.	(% increase / mm.Hg CO_2.)		% change.
range	3.00 to 8.24	3.00 to 8.24	3.20 to 8.26	-3 to +16
mean	4.68	4.75	4.78	+1
SD	1.47	1.89	1.85	
SE	0.32	0.71	0.70	1

No significant change in slope with airways restriction.

average rate of EMG response.	(% increase / mm.Hg. CO_2)		% change.
range	6.10 to 16.60	6.10 to 16.6	5.73 to 15.71	-6 to +3
mean	8.96	9.81	9.63	-1
SD	3.14	4.22	4.03	
SE	0.68	1.59	1.52	1

No significant change in slope with airways restriction

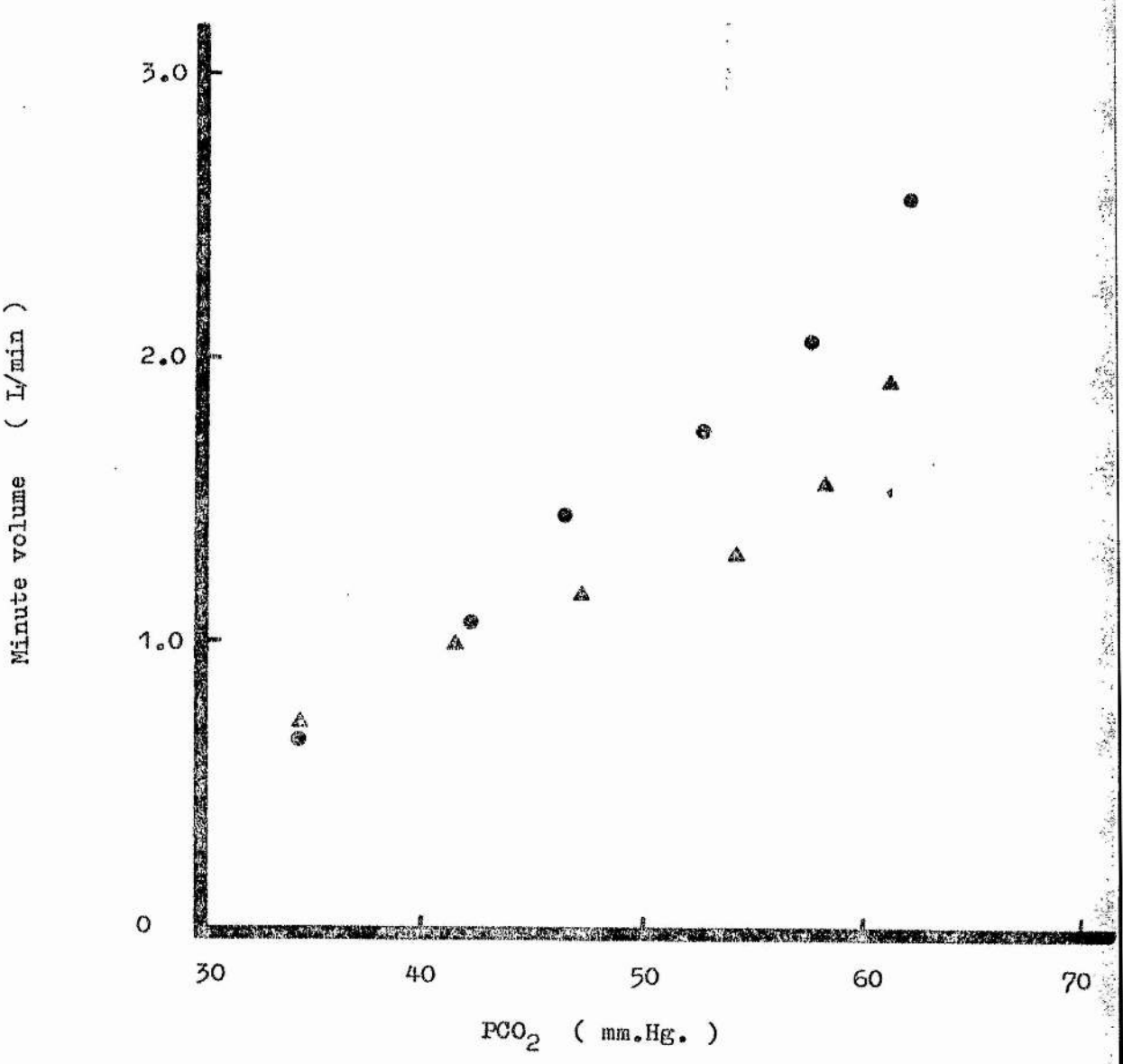


Fig. 1B-1

Graph of ventilation plotted against rising PCO_2 during CO_2 rebreathing in a representative rabbit (rabbit 3, observation 7)

● no resistance. slope= 66.6 $ml.min^{-1}$ $mm.Hg.CO_2^{-1}$

▲ added resistance. slope= 42.1 $ml.min^{-1}$ $mm.Hg.CO_2^{-1}$

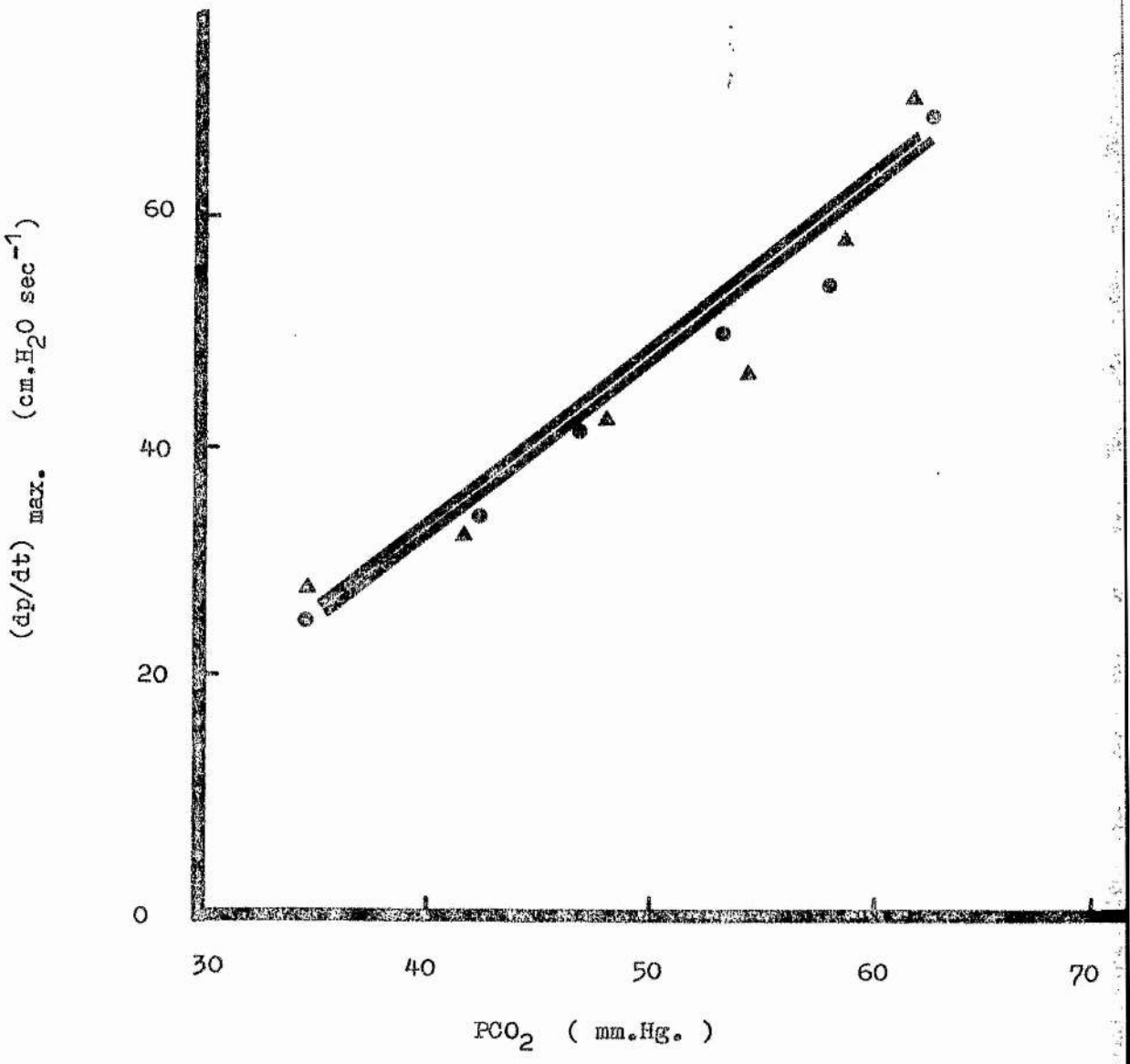


Fig. 1B-2

Graph of $(dp/dt)_{max.}$ plotted against rising PCO_2 during CO_2 rebreathing in rabbit 3 (observation 7).

● no resistance slope= 1.53 $cm.H_2O\ sec^{-1} mm.Hg.CO_2^{-1}$

▲ added resistance slope= 1.56 $cm.H_2O\ sec^{-1} mm.Hg.CO_2^{-1}$

Total EMG response

There was a linear relationship between total EMG and end-tidal PCO_2, the total electrical activity increasing with increasing PCO_2.

The total EMG response as measured by Δtotal EMG/Δ PCO_2 ranged from 3.00 to 8.24% increase/mm.Hg.CO_2 (mean 4.68 SD 1.47 SE 0.32). With the addition of restriction, there was increase in absolute values of total EMGs at all levels of PCO_2. However, the response slopes with and without resistance were not significantly different. (Fig. 1B-3).

Total EMG/$T_{insp.}$ (or average EMG activity) response

During unrestricted breathing there was a linear relationship between the average EMG activity and end-tidal PCO_2.

There was a corresponding increase in $T_{insp.}$ with restriction compared with unrestrictive breathing. The response slope did not show a significant difference during unrestricted and restricted breathing. At all levels of PCO_2, the absolute values of total EMGs/$T_{insp.}$ did not show a difference between restricted and unrestricted breathing. The average EMG response ranged from 6.10 to 16.60%/mm.Hg.CO_2. (mean 8.96 SD 3.14 SE 0.68). (Fig. 1B-4).

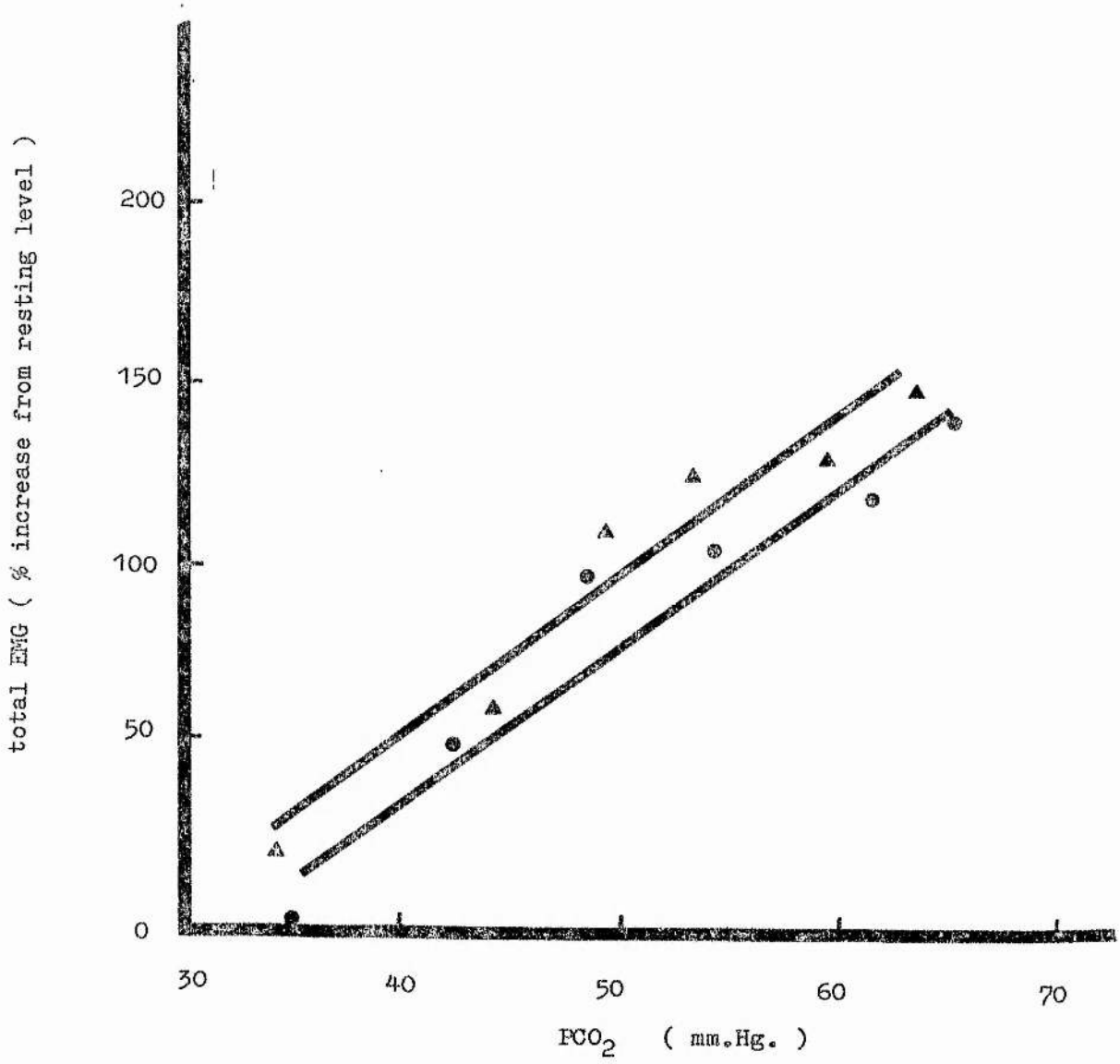


Fig. 1B-3

Graph of total EMG plotted against rising PCO_2 during CO_2 rebreathing in a representative rabbit (rabbit 1, observation 1)

● no resistance. slope= 4.38 % increase / mm.Hg.CO_2

▲ added resistance. slope= 4.54 % increase / mm.Hg.CO_2

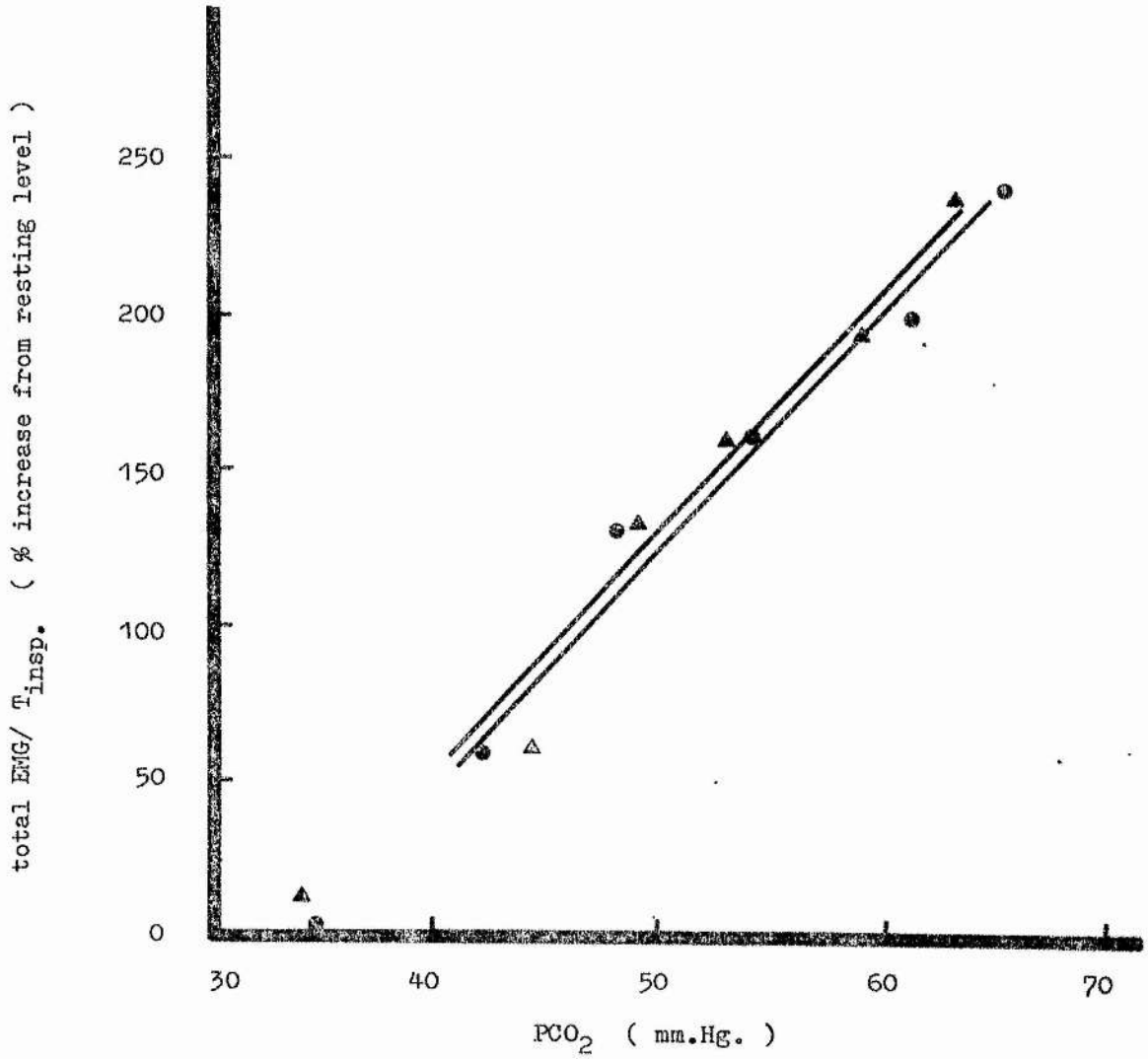


Fig. 1B-4

Graph of average EMG electrical activity plotted against rising PCO_2 during CO_2 rebreathing in a representative rabbit (rabbit 1, observation 1)

● no resistance. slope= 7.87 % increase/ mm.Hg.CO_2

▲ added resistance. slope= 7.92 % increase/ mm.Hg.CO_2

Correlation between ventilatory and $(dp/dt)_{max}$. responses to CO_2.

There was a significant correlation between the two responses measured ($r = 0.859$ $p = <0.001$) when there was no airways restriction. Since there was a significant reduction only in ventilatory response with restriction, no correlation was made after restriction, between the two measures. (Fig. 1B-5).

Correlation between ventilatory and total EMG responses to CO_2.

There was a significant correlation between the two responses measured without airways restriction ($r = 0.845$ $p = <0.001$). Again no correlation was made of the responses during airways restriction. (Fig.1B-6).

Correlation between ventilatory and average EMG activity (total EMG/$T_{insp.}$) responses to CO_2.

There was a significant correlation between the two responses, without airways restriction ($r = 0.831$ $p = <0.001$). No correlation made during airways restrictive breathing. (Fig. 1B-7).

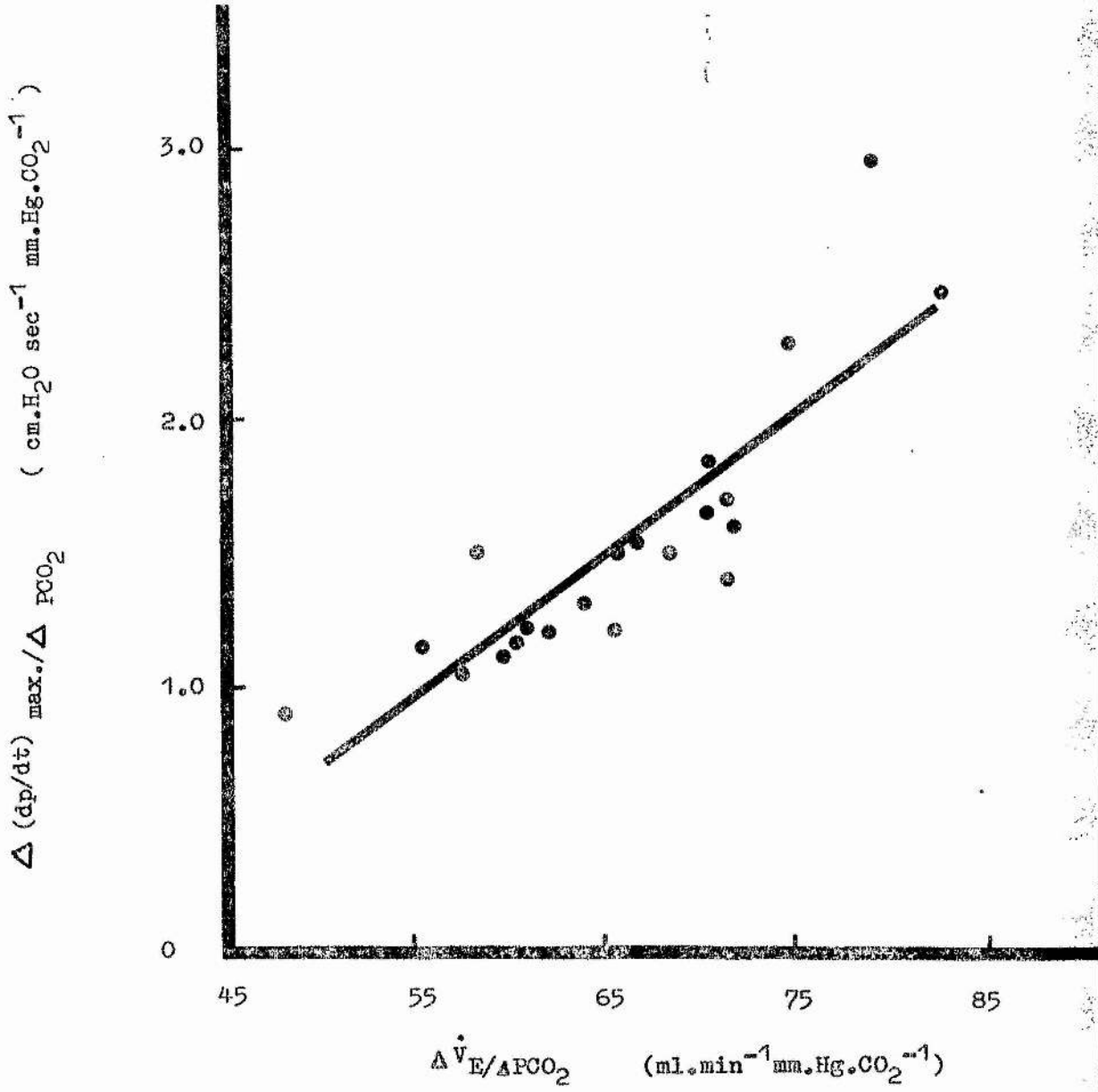


Fig. 1B-5

Relationship between $(dp/dt)_{max.}$ and ventilatory responses to CO_2 in 21 observations from 7 rabbits. There was no resistance added. Each point represents one observation.

$r = 0.859$

$p = < 0.001$

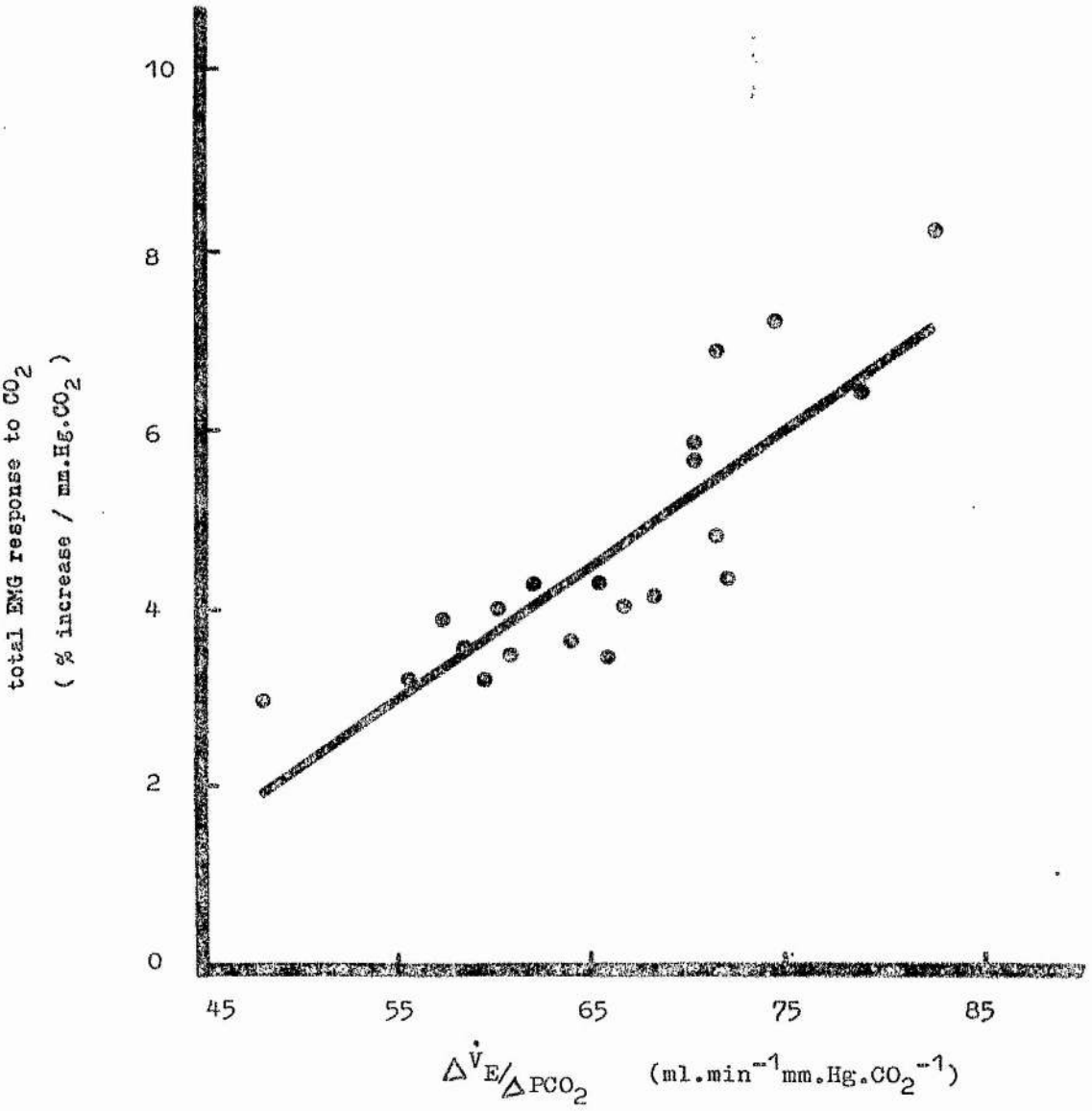


Fig. 1B-6

Relationship between total EMG electrical activity and ventilatory responses to CO_2 in 21 observations from 7 rabbits. There was no resistance added. Each point represents one observation.

r= 0.845

p= < 0.001

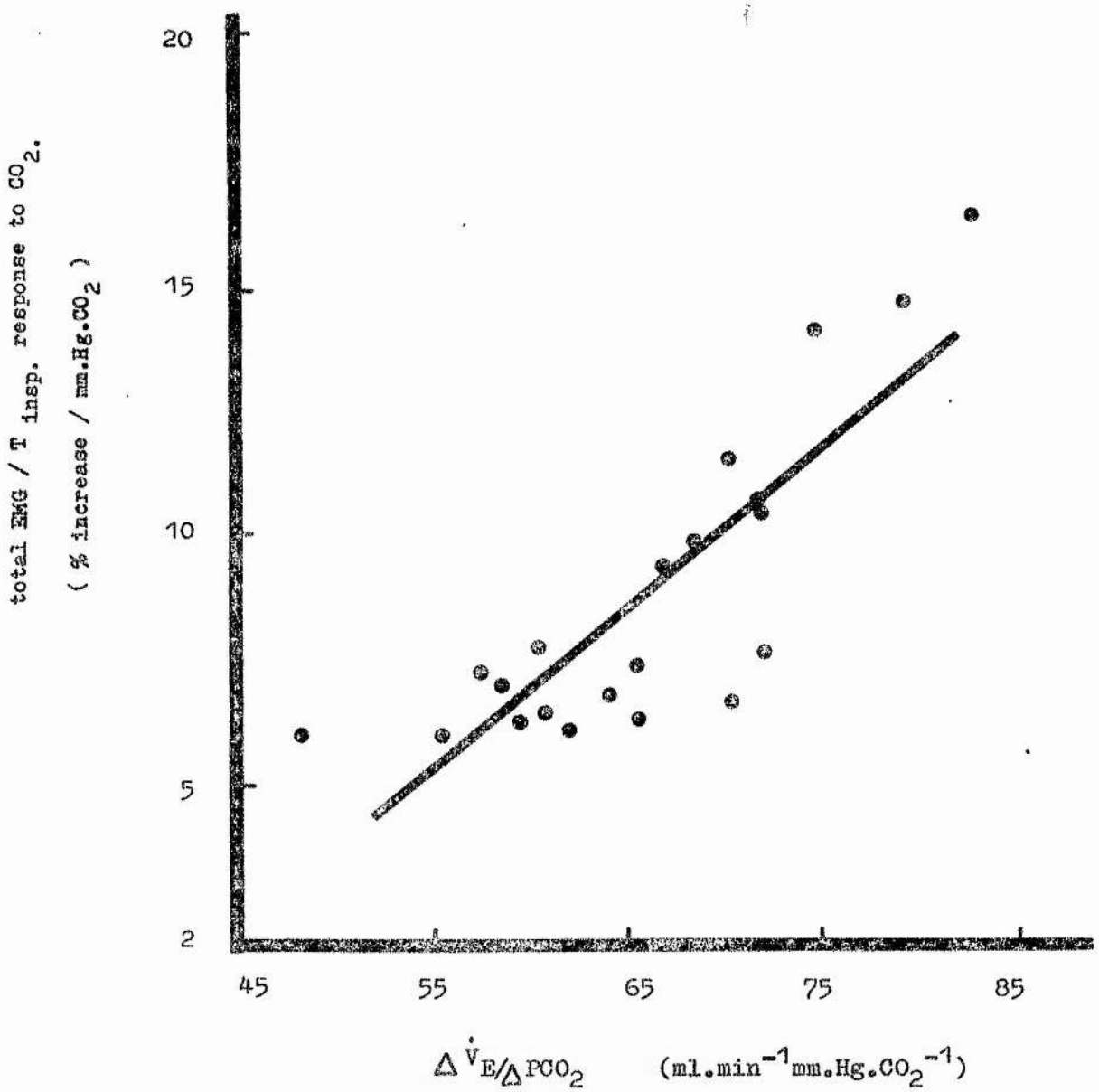


Fig. 1B-7

Relationship between average EMG electrical activity and ventilatory responses to CO_2 in 21 observations from 7 rabbits. There was no added resistance. Each point represents one observation.

r= 0.831

p= < 0.001

Correlation between $(dp/dt)_{max.}$ and total EMG responses to CO_2.

There was a significant correlation between the two responses, without airways restriction (r= 0.790 p = <0.001) (Fig. 1B-8). With airways restriction, there was also a significant correlation (r= 0.885 p= <0.01). (Fig.1B-9).

Correlation between $(dp/dt)_{max.}$ and total $EMG/T_{insp.}$ responses to CO_2.

There was a significant correlation between the two responses during unrestricted breathing (r= 0.886 p= <0.001) (Fig.1B-10). With restriction there was still a significant correlation between the two responses (r= 0.948 p= < 0.001). During both unrestricted and restricted airways breathing, the correlation between $(dp/dt)_{max.}$ and total $EMG/T_{insp.}$ responses were more significant than that between $(dp/dt)_{max.}$ and total EMG responses. (Fig.1B-11).

Correlation between $(dp/dt)_{max.}$ and total EMGs.

There was a significant correlation between $(dp/dt)_{max.}$ and total EMGs in all the rabbits while breathing without resistance. At all levels of PCO_2, the changes in

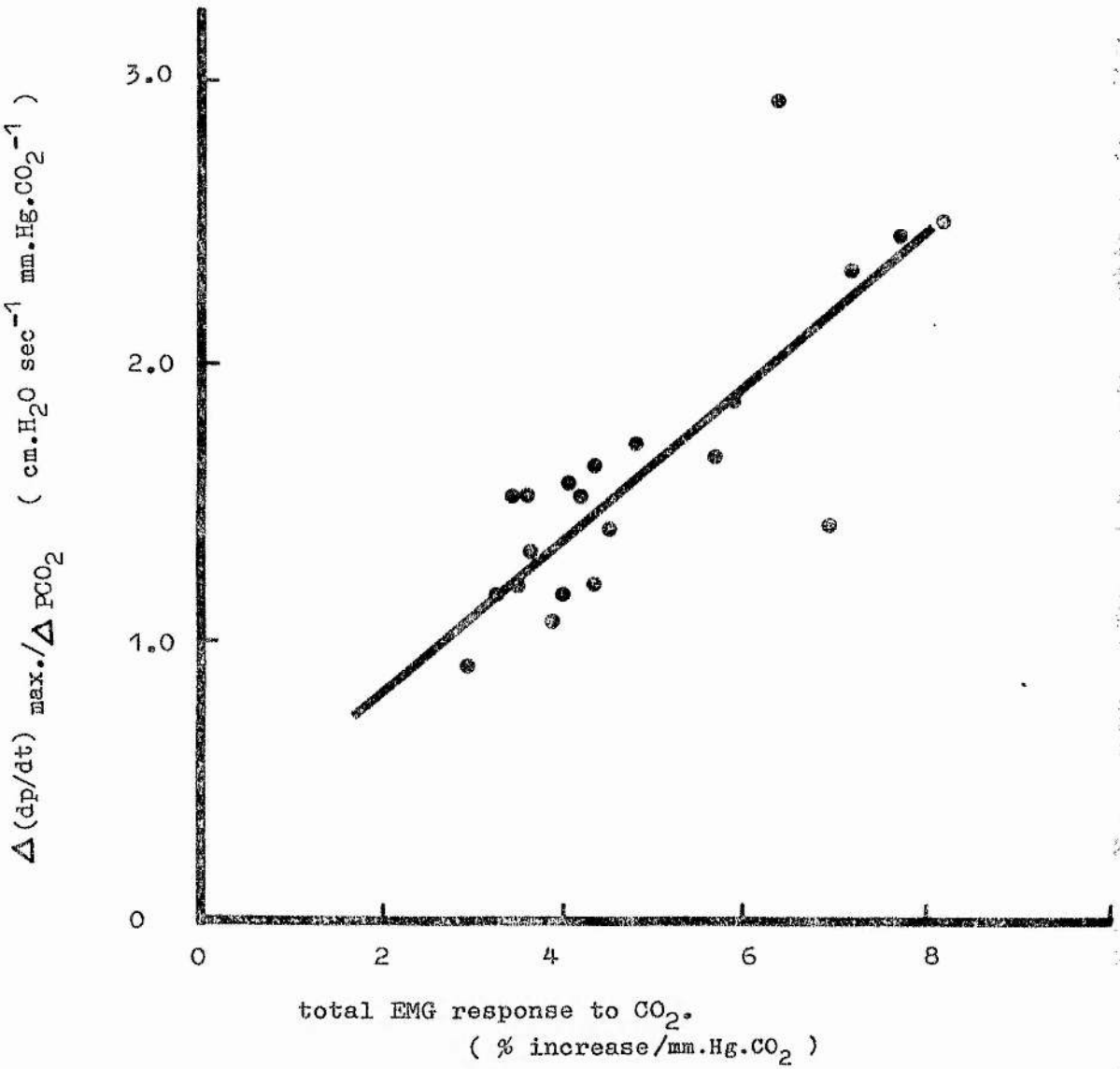


Fig. 1B-8

Relationship between $(dp/dt)_{max.}$ and the total EMG electrical activity responses to CO_2 in 21 observations from 7 rabbits. There was no resistance added. Each point represents 1 observation.

$r = 0.790$

$p = < 0.001$

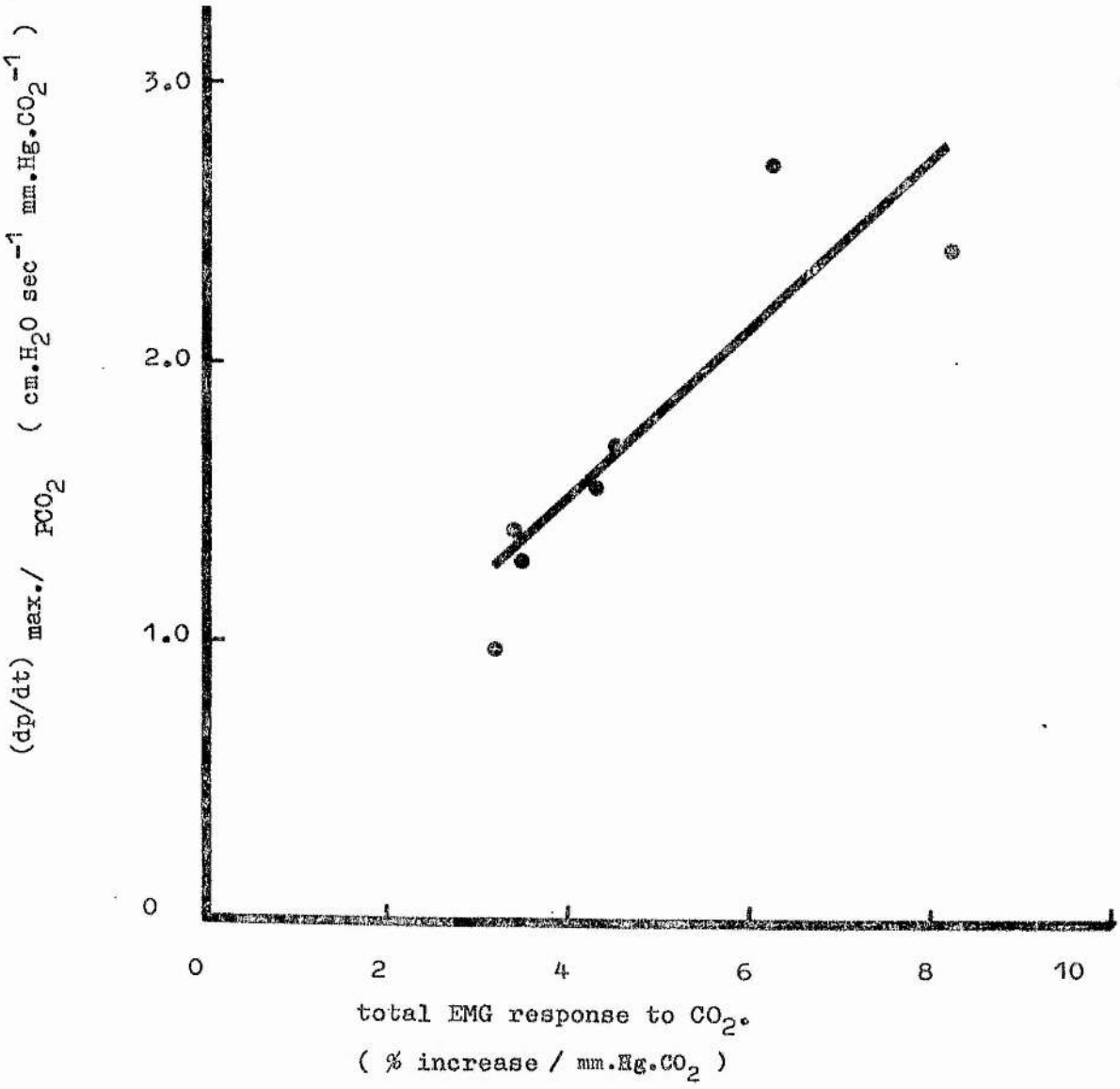


Fig. 1B-9

Relationship between $(dp/dt)_{max.}$ and the total EMG electrical activity responses to CO_2 in 21 observations from 7 rabbits, with added resistance. Each point represents 1 observation.

$r = 0.885$

$p < 0.01$

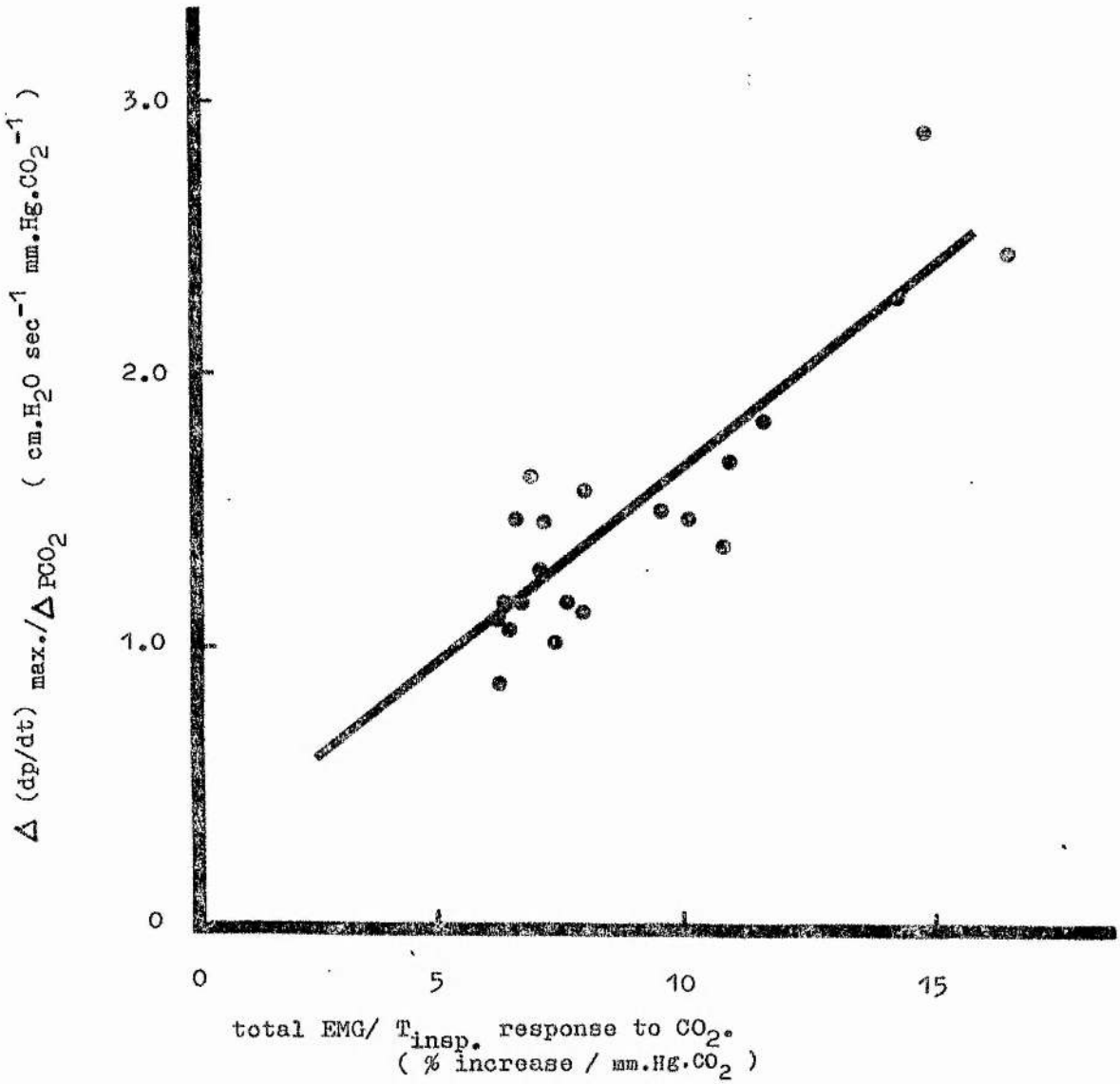


Fig. 1B-10

Relationship between $(dp/dt)_{max.}$ and average EMG electrical activity responses to CO_2 in 21 observations from 7 rabbits. There was no resistance present. Each point represents 1 observation.

$r = 0.886$

$p < 0.001$

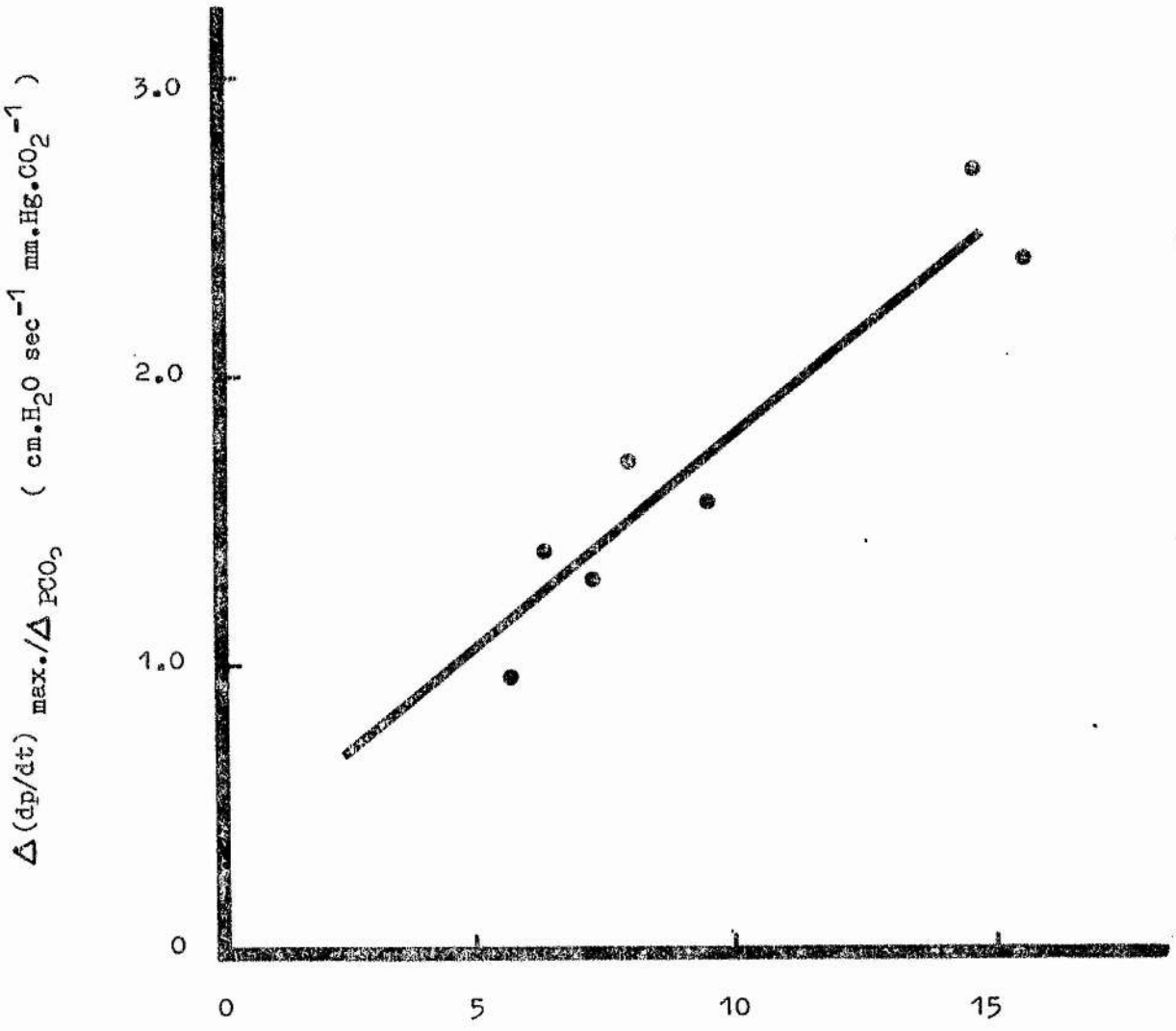


Fig. 1B-11

Relationship between $(dp/dt)_{max.}$ and average EMG electrical activity responses to CO_2 in 21 observations from 7 rabbits, with added resistance. Each point represents 1 observation.

$r = 0.948$

$p = < 0.001$

$(dp/dt)_{max.}$ paralleled the changes in total EMGs. In all the rabbits tested, the regression coefficient was more than 0.900 and $p = < 0.001$.

During resistance breathing similar correlations and results were obtained. (Fig. 1B-12).

Correlations between $(dp/dt)_{max.}$ and total EMGs/$T_{insp.}$

There was a significant correlation between $(dp/dt)_{max.}$ and the average EMGs during unrestricted breathing in all the rabbits studied. The changes in $(dp/dt)_{max.}$ paralleled the changes in the average EMGs at all levels of PCO_2. In all the rabbits tested, the regression coefficient between the two changes were more than 0.950 and $p = < 0.001$.

Similar correlations and results were obtained for restricted breathing. (Fig. 1B-13).

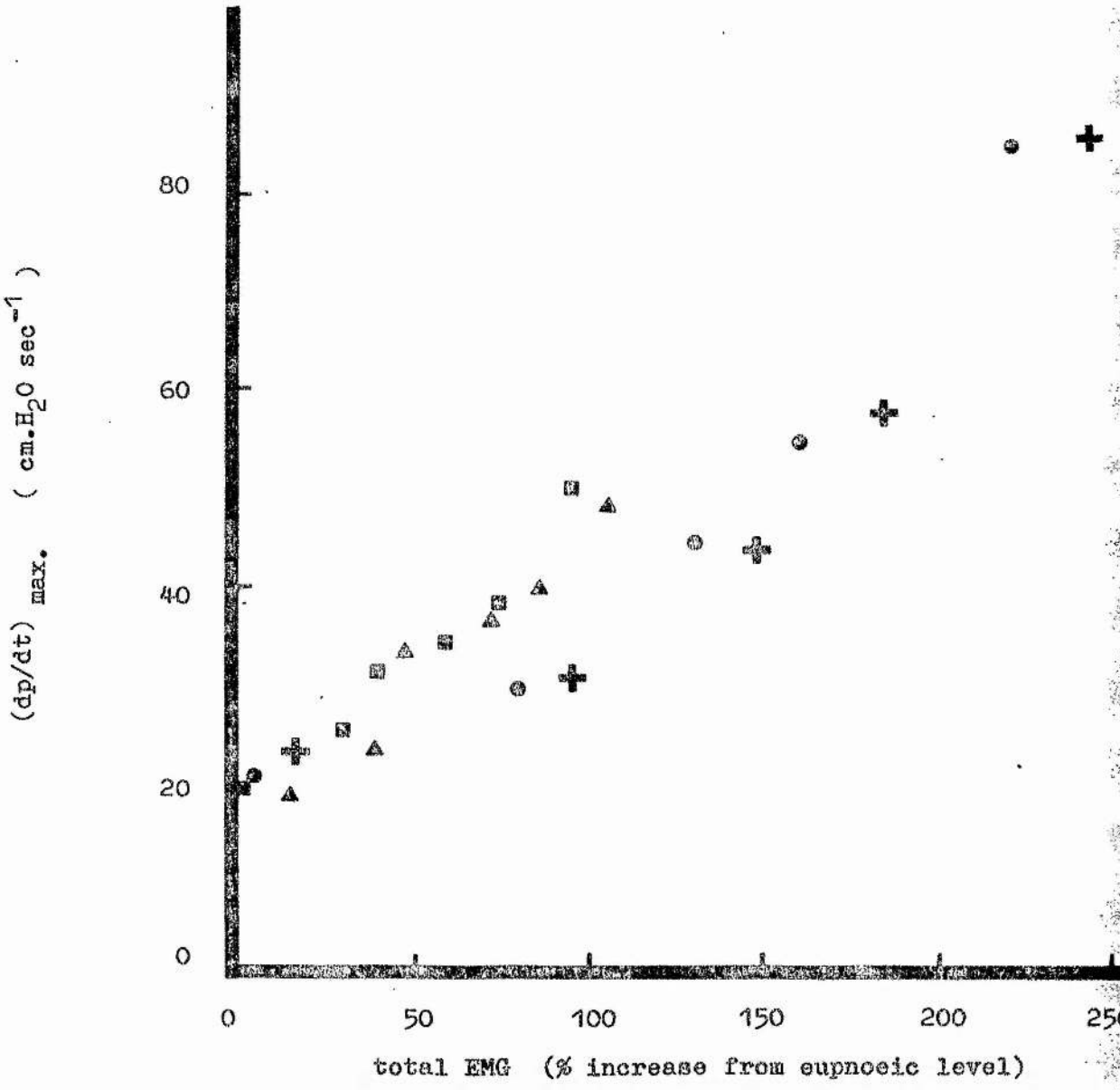


Fig. 1B-12

Relationship between $(dp/dt)_{max.}$ and total EMG electrical activity in 2 representative rabbits, during CO_2 rebreathing. Each point represents the corresponding $(dp/dt)_{max.}$ and total EMG activity values at a particular PCO_2.

▲ with resistance	r= 0.973	p= < 0.001	rabbit 5
■ without resistance	r= 0.971	p= < 0.001	
✚ with resistance	r= 0.950	p= < 0.001	rabbit 7
● without resistance	r= 0.958	p= < 0.02	

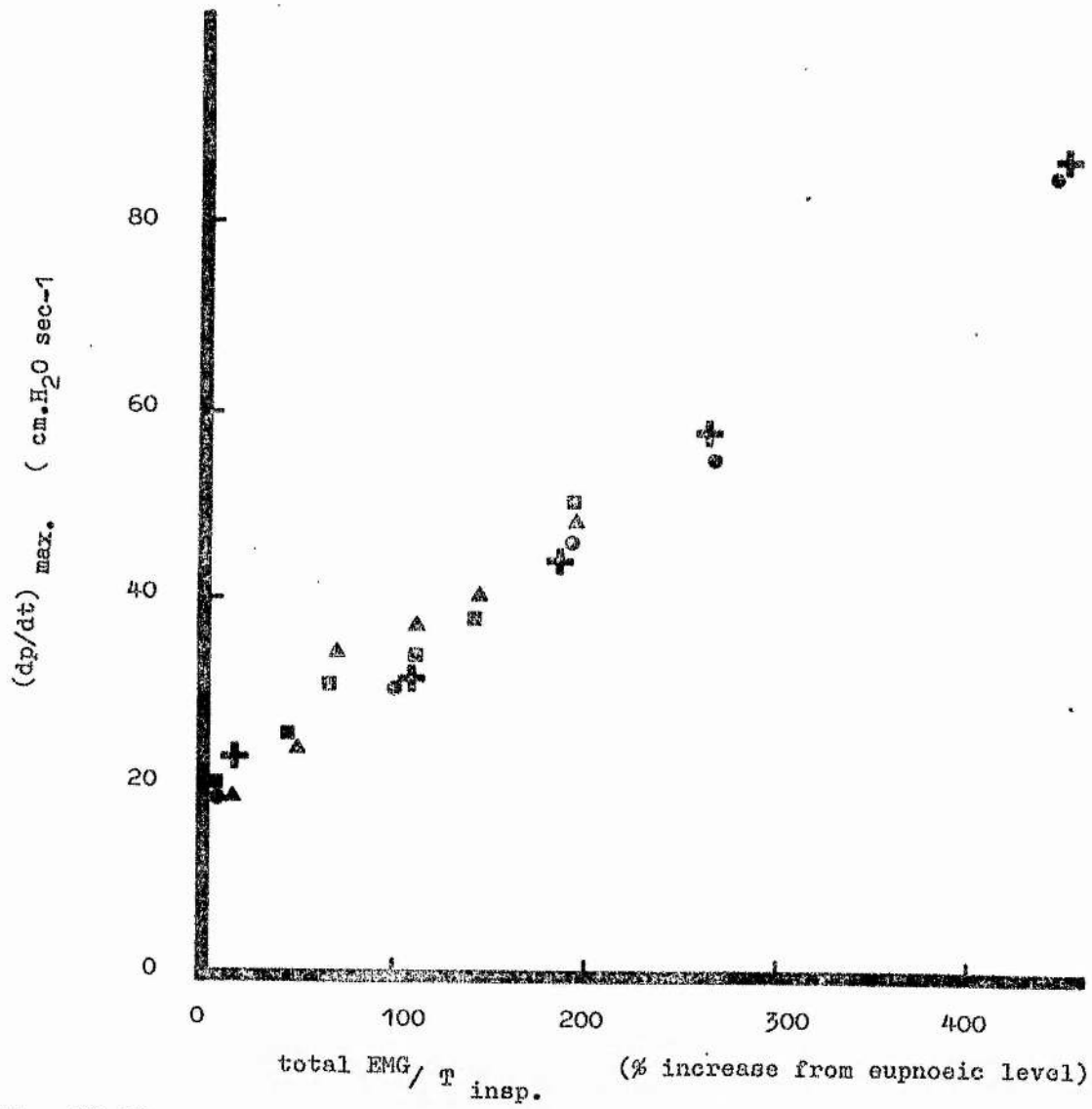


Fig. 1B-13

Relationship between $(dp/dt)_{max.}$ and the average EMG electrical activity in 2 representative rabbits, during CO_2 rebreathing. Each point represents the corresponding $(dp/dt)_{max.}$ and the average EMG activity values at a particular PCO_2.

▲ with resistance	r= 0.970	p=<0.001	rabbit 5
■ without resistance	r= 0.985	p=<0.001	
✚ with resistance	r= 0.995	p=<0.001	rabbit 7
● without resistance	r= 0.996	p=<0.001	

DISCUSSION

The main aim of the experiment was to study the $(dp/dt)_{max.}$ response to CO_2 in relation to the electrical activity of the diaphragm and also the corresponding relation with ventilatory response.

The strength of muscle contraction is a function of the number of motor units firing. Thus in the diaphragm it has been shown that increasing phrenic nerve activity causes increased diaphragmatic electrical activity. However, it is difficult to quantify the strength of the muscle contraction by calculating the number of firings alone as the size of the motor units varies and this will cause variation in action potentials. However, when the electromyogram signal is integrated, it gives a function of both the mean size of the action potentials recorded as well as their firing rate. Thus integrated EMGs give a reliable relationship to the force of muscle contraction. Lippold 1952 has shown that the force produced by an isometrically and submaximally contracting muscle was linearly related to the mean rate of integrated EMG activity.

Direct diaphragmatic electrical activity in animals has been studied by Shannon and Zechman 1972 and Altose et al., 1975. They found that with increase in PCO_2, there was a corresponding increase in diaphragmatic electrical activity. Direct measurements from the phrenic nerves have also been studied by Iscoe et al., 1976 during normal air breathing, and by Evanich et al., 1976 during CO_2 rebreathing. These authors showed increased activity

with increasing PCO_2. Eldridge 1971, showed that in anaesthetised cats, with an increase in tidal volume, the size of phrenic nerve action potential increased, and these correlated with the diaphragmatic motor unit activity. Lourenco et al., 1966 showed that during unobstructed breathing, tidal volumes are proportional to the phrenic nerve and diaphragm electrical activity. However, with inspiratory loading, tidal volume decreases even though phrenic nerve and diaphragmatic activity increases.

In this study there was linear relationship between ventilation, $(dp/dt)_{max.}$, total EMG activity and average EMG activity with end-tidal PCO_2; the values increasing with increase in PCO_2. This suggests that all the variables measured with increasing PCO_2, would be reliable as CO_2 response index. However, with added restriction, there was a significant reduction in ventilatory response to CO_2.

In this study as in that of Altose et al., 1975, it was seen that with resistive loading, the diaphragmatic activity increased with hypercapnia. Although when total EMGs response to CO_2 slopes were the same with and without restriction, the absolute values for total EMGs was greater at all levels of PCO_2 with restriction present. However, this increase in diaphragmatic activity was accompanied by corresponding increase in inspiratory duration. When total EMGs were divided by $T_{insp.}$ to

give the average rate of diaphragmatic electrical activity, there was no significant difference in the response to CO_2 with and without restrictive loading. Similarly the $(dp/dt)_{max.}$ response to CO_2 was unaffected by airways restriction. This suggests that whilst ventilatory response would not reflect CO_2 drive in the face of airways restriction, total EMG activity, average EMG activity and $(dp/dt)_{max.}$ response would be a reliable index of CO_2 chemosensitivity even with restriction.

During CO_2 rebreathing, when $(dp/dt)_{max.}$ was plotted against total EMG activity, a linear relationship, increase in $(dp/dt)_{max.}$ with increasing total EMG activity, was found both in unrestricted and restricted breathing in all the rabbits studied. Thus changes in $(dp/dt)_{max.}$ parallel changes in total EMG activity. Similar linear relationship was found for $(dp/dt)_{max.}$ and total $EMG/T_{insp.}$ both during unrestricted and restricted breathing. Evanich et al., 1976 found that with airways occlusion in anaesthetised cats, the changes in phrenic nerve activity (expressed as "moving time average") paralleled the changes in intratracheal occlusion pressure both in air as well as CO_2 rebreathing. Similarly Eldridge 1975 found that there was a linear relationship between occlusion pressure and the average level of activity computed over 100 ms intervals. Since it is found in this study that there were parallel changes in both diaphragm and $(dp/dt)_{max.}$ in hypercapnia,

it suggests that $(dp/dt)_{max.}$ reflects respiratory neuron activity, in anaesthetised rabbits. Thus $(dp/dt)_{max.}$ can be said to be an index of muscle force generation and respiratory control output.

Richardson and Widdicombe 1969 found that the ventilatory response curve in both anaesthetised and unanaesthetised rabbits to be linear, which agrees with findings in this study. However, Richardson and Widdicombe 1965 and 1969 have shown that the position and shape of end-tidal PCO_2/min. volume curve (i.e. ventilatory response to CO_2) in rabbits depended on the presence or absence of anaesthesia. With anaesthesia, the ventilatory response curve was slightly reduced. In this study since all the tests were carried out in anaesthetised rabbits, and no relative comparison was made between CO_2 responses in unanaesthetised and anaesthetised animals, it would not affect the significance of the results.

In this study, the electrode was not removed throughout the whole test in the same rabbit. An attempt was made to place the electrode in similar position in each rabbit to produce as little EMG activity variations as possible. Any variation in placement would not produce a significant difference as Boyd and Basmajian 1963 have shown that different electrode positions on the same rabbit's diaphragm produced only minor variations in degree of recorded diaphragmatic activity. The diaphragm seems

to function as a unit with all its portions contracting simultaneously.

Zechman et al., 1957 have shown that the functional residual capacity may be increased by flow resistive loading during both inspiration and expiration but does not show any change with flow resistive loading during inspiration alone. However, Altose et al., 1975 have shown that in dogs, both types of loadings gave similar EMG activity. They suggested that any changes in resting lung volumes due to the loading has no appreciable effects on EMG activity. In this study no determination of resting lung volumes was made. However, since this study employed methods similar to Altose et al., 1975, any changes in lung volume that might occur with loading would not show any effects on the EMG activity.

In conclusion, this study has shown that whilst airways restriction did cause a significant reduction in the ventilatory response to CO_2; $(dp/dt)_{max.}$, total EMG electrical activity and the mean rate of EMG electrical activity responses to CO_2 were unaffected by airways obstruction. It has also been shown that changes in $(dp/dt)_{max.}$ paralleled changes in both total EMGs and average rate of EMG activity during unrestricted and restricted breathing. This finding provides further evidence that $(dp/dt)_{max.}$ response to CO_2 can be used as a reliable index of CO_2 responsiveness unaffected by airways restriction.

SECTION 2

CHEMOSENSITIVITY AND EXERCISE VENTILATORY RESPONSE IN NORMAL SUBJECTS.

INTRODUCTION.

There have been numerous reports of differences in sensitivity to hypercapnia and hypoxia amongst normal subjects. Thus Hurtado 1960 and Severinghaus et al 1966 found that natives of high altitudes have lower ventilatory response to hypoxia than sea-level dwellers. These natives too showed a lower ventilatory response to CO_2.(Sorensen and Cruz 1969). Amongst normal subjects residing at sea-level too there is a wide variation in ventilatory response to hypercapnia (Read 1967, Godfrey et al 1971, Jennett and Short 1973 and Hirshman et al 1975) and hypoxia (Rebuck et al 1973 and Hirshman et al 1975). A positive correlation between hypercapnic and hypoxic ventilatory responses was shown by Byrne-Quinn et al 1971, Rebuck et al 1973 and Hirshman et al 1975 in normal subjects.

Godfrey et al 1971 did not find any significant difference in the hypercapnic and hypoxic ventilatory responses of athletes and non-athletes normals. However, Byrne-Quinn et al 1971 have shown that athletes showed a significantly lower hypercapnic and hypoxic ventilatory response compared with non-athletes.

Rebuck et al 1972 have shown that in 9 normal subjects, those showing a low chemosensitivity to CO_2 also showed a low ventilatory response to exercise (when exercise is expressed as CO_2 produced or O_2 uptake).

Similarly Spiro et al 1974 suggested that the $\Delta V_E/\Delta VO_2$ slope obtained during exercise may be used as a physical

fitness index with unfit subjects showing steeper slope. Wasserman et al 1973 has shown that the linear part of $\Delta \dot{V}_E/\Delta \dot{V}O_2$ and $\Delta V_E/\Delta VCO_2$ slopes (the slopes of ventilatory response to exercise) breaks (Anaerobic threshold) earlier in unfit normal subjects. This break appears coincident with the appearance of anaerobic metabolism which occurs at a lower load in less fit subjects, suggesting that it may be used as an index of physical fitness.

In this study a larger group of normal subjects were tested for their CO_2 ventilatory response and ventilatory response to exercise. The subjects were made up of trained (i.e. in various sporting activities) and untrained normal subjects. Measurements of maximum oxygen uptake ($\dot{V}O_2$ max.) and the 'anaerobic threshold' (used as physical fitness indices) were made to investigate their relationship with CO_2 and exercise ventilatory response.

In some of the subjects, the ventilatory and $(dp/dt)_{max.}$ response to hypoxia was measured. Similarly some of the subjects' CO_2 response was measured in terms of $(dp/dt)_{max.}$. Thus the relationships between $(dp/dt)_{max.}$ and ventilatory response to hypoxia and hypercapnia and exercise ventilatory response were studied.

SUBJECTS AND METHODS.

Subjects.

47 normal males (aged 18 to 27) were used in this study. Ten of the subjects were in training and undergoing various sorts of regular sporting activities. All the subjects underwent both the exercise and CO_2 response test and of these subjects, the 11 untrained also underwent an isocapnic hypoxia test. An electrically braked cycle ergometer was used, with the load increased stepwise. The subject was first familiarised with using a nose-clip and breathing through the mouthpiece for 5 minutes prior to the exercise. None of the subjects had any exercise for at least 30 minutes before the test, to stabilise his breathing pattern.

After 5 minutes, the subject sat on the cycle ergometer and necessary adjustments made to the height of the pedals and mouthpiece. No unnecessary discomfort must be present as it might disturb his breathing during later high loads of exercise. A further 5 minute rest period with the mouth connected to the circuit was necessary, for breathing stabilisation. This ensured thorough mixing of the expired gas as well as keeping his CO_2 and tidal sample within $\pm$ 1 mm.Hg. variation. The subject then started to pedal at 100 kpm load keeping the pedal frequency at 60 rpm for 2 to 3 minutes, until a steady state is reached. The load was then increased at 100 kpm every 1 minute until he becomes exhausted.

The CO_2 response test at rest was done on the same day but 3 to 4 hours after, the exercise experiment. The isocapnic hypoxia experiment took place within a week of the exercise and CO_2 response tests.

6 subjects repeated the exercise test within one week. Repeats of CO_2 and hypoxia response tests are discussed in Section 1A.

Equipments.

All subjects were weighed and their FVC, FEV and VC measured using the Vitalograph Single Breath Instrument.

a) Exercise. (Fig. 2-a)

An electrically braked Cycle Ergometer (ELEMA-SCHONANDER AM 368) was used for the exercise test. Stepwise increases of 100 kpm up to a maximum of 2000 kpm can be used. A mouthpiece was fitted to a low resistance two-way valve (dead space of 140 ml), with outlet of the valve going to a mixing chamber, volume 6 litres. A pneumotachograph was attached to the inlet side of the valve, the inspired flow measured by a Mercury Electric Manometer (accuracy of $\pm$) and the signal integrated. Inspired ventilation was measured for each tidal volume and used later for measuring inspiratory and expiratory duration in Section 3. The resistance for the inspired side was 2.0 cm.H_2O and expired side was 1.1 cm.H_2O at a flow rate of 3 litres sec.$^{-1}$.

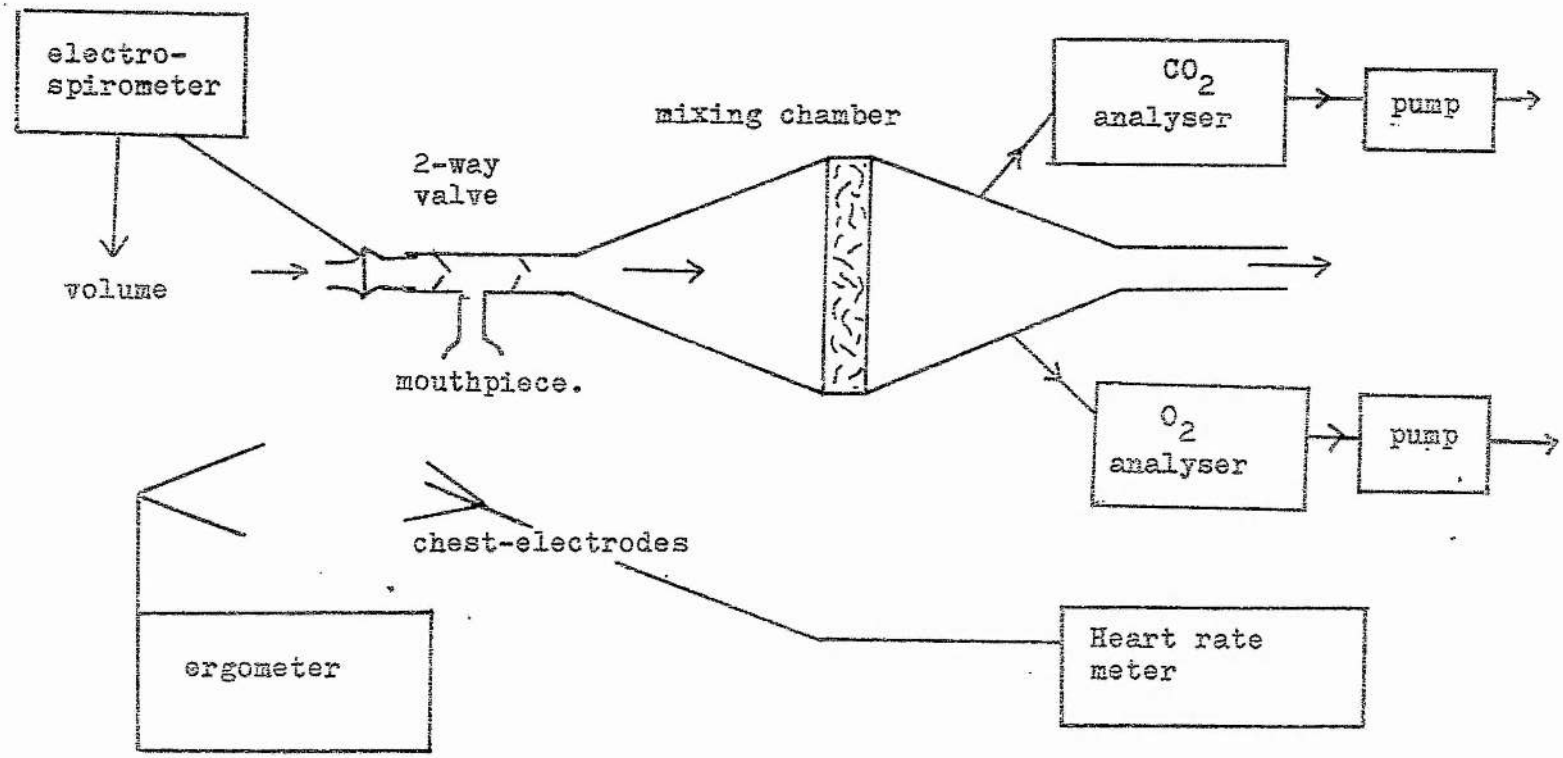


Fig. 2-a Diagram of apparatus used in the exercise study.

The mixing chamber consisted of two separate halves with a gauze midwall for thorough mixing. In the second half of the chamber where air is thoroughly mixed, there are two small outlets, one for O_2 measurement and the other for CO_2 measurement. For CO_2 measurement, a sample of air at a flow rate of 500 $ml.min^{-1}$ was passed through a Beckman CO_2 Infra Red Medical Gas Analyser (Model LB 1). The gas analyser (accuracy $\pm$ 1% of meter-range of 0 to 10% CO_2) was calibrated using several gas mixtures which was first analysed by Lloyd-Haldane apparatus. The CO_2 meter was switched on overnight prior to the test for greater stability. The O_2 meter (Paramagnetic-Servomex type OA 272) has air sample flowing at the rate of 200 $ml.min^{-1}$. Calibration of both meters was made every morning before a set of experiments were carried out later in the day. To monitor heart rate, 3 point chest electrodes are used and connected to a pen-recorder (DEVICES AC1 Pre-Amp with Sub 3 ECG sub-unit). Simultaneous measurements of ventilation, heart rate, CO_2% and O_2% were made and recorded on a Devices four channel pen-recorder.

b) CO_2 Response Test.

For this test, the same circuit, equipments and method were employed as in Section 1A.

In 16 subjects (untrained) in addition to ventilatory response, the maximum rate of development of pressure during occlusion, $(dp/dt)_{max.}$, was measured; the mouth pressure signals differentiated into spikes which was recorded onto

a fast-responding pen-recorder (GOULD BRUSH). (Section 1A). Rebreathing was continued for 4 to 5 minutes or until the subject cannot continue longer. Repeat tests are discussed in Section 1A.

c) Response to Hypoxia.

For the hypoxia study at rest, details of the setup and method is discussed in Section 1A. The experiment took about 5 to 6 minutes. During the experiment CO_2 and O_2 was measured continously by gas meters and minute volume measured by an electro-spirometer. The change in mouth pressure was measured and differentiated to give $(dp/dt)_{max.}$ values.

11 subjects (untrained) underwent the test.

FORMULAE USED and CALCULATIONS.

The following formulae are used throughout the calculations.

$$\dot{V}_E = \frac{\dot{V}_I \times F_I N_2}{1.00 - (F_E CO_2 + F_E O_2)}$$

$$\dot{V}_I O_2 = \dot{V}_I \times 0.2093$$

$$\dot{V}_E O_2 = \frac{\dot{V}_I \times 0.7903}{1.00 - (F_E CO_2 + F_E O_2)} \times F_E O_2$$

$\dot{V}O_2 = \dot{V}_I O_2 - \dot{V}_E O_2$

$\dot{V}CO_2 = F_E CO_2 \times \dot{V}_I \times 0.897$

All values were corrected to STPD and BTPS as required.

TREATMENT OF DATA.

For CO_2 rebreathing and hypoxic response tests, details of treatment of data are given in Section 1A.

In the exercise study, the simultaneous readings of CO_2, O_2, heart rate and ventilation were recorded on a four channel pen-recorder, at a speed of 5 mm/sec. The record was divided into one minute divisions, each corresponding to an increase in load of 100 kpm ;(as shown in Fig. 2-b). CO_2 and O_2 concentrations were calibrated before the experiments and marked on the recording paper. Ventilation was calibrated using a one litre syringe attached to the pneumotachograph. Heart rate was obtained from the recorded E.C.G.

CO_2 and O_2 readings were taken over the last quarter of each minute. Tidal volume measurements for one minute were added to give minute ventilation. The heart rate was measured during the last half minute of exercise.

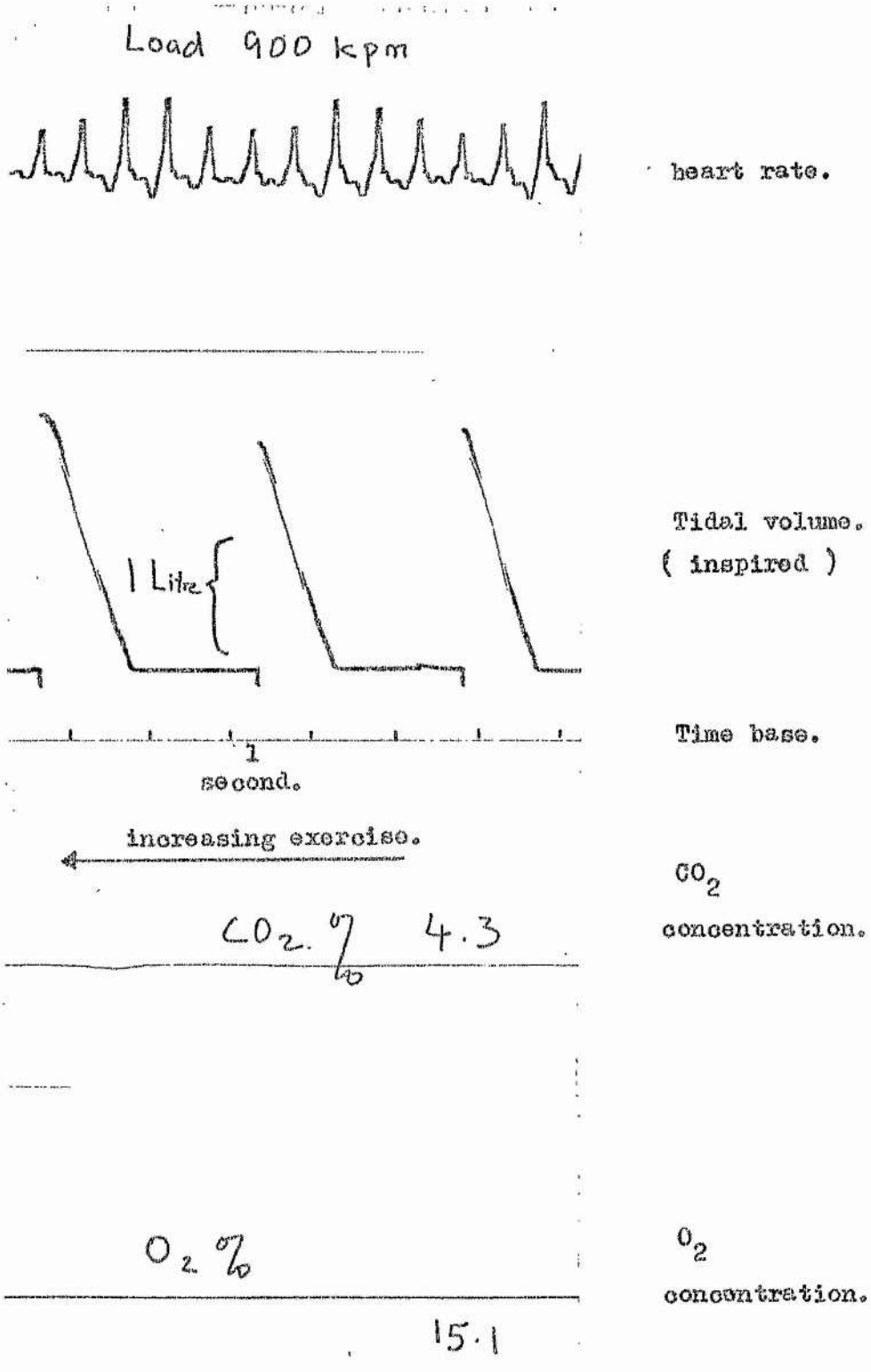


Fig. 2-b. Typical trace of simultaneous recordings made during progressive exercise test.

Number of subjects in different tests.

In this study the number of subjects used for different tests varied. In all 47 subjects (trained and untrained), the slope 'S' ($\Delta \dot{V}_E / \Delta PCO_2$) or responsiveness to CO_2, ventilatory response to exercise (when exercise expressed both as oxygen uptake and CO_2 produced) and a prediction of $\dot{V}O_2$ max. was obtained. 11 subjects (untrained) from the 47 subjects underwent measurement of hypoxic response, measurements being made both in terms of $\Delta \dot{V}_E / \Delta (1/PAO_2 - 32)$ $L.mmHg.min^{-1}$ and $\Delta(dp/dt)_{max.} / \Delta (1/PAO_2 - 32)$ $cm.H_2O$ $mm.Hg$ s^{-1}, and their measurements of 'S' by both $\Delta \dot{V}_E / \Delta PCO_2$ and $\Delta(dp/dt)_{max.} / \Delta PCO_2$. 16 subjects (untrained) from the 47 had their their 'S' measured both in terms of ventilatory and $(dp/dt)_{max.}$ response.

5 untrained and 1 trained subjects repeated the exercise test within 2 weeks to test the variation obtained between the first and second readings of the exercise ventilatory responses. Repeats for the CO_2 rebreathing and hypoia tests are discussed in Section 1A.

RESULTS.

The 47 normal subjects were made up of 10 trained and 37 untrained subjects. There was overlapping of results as far as CO_2 responsiveness, ventilatory response to exercise and $\dot{V}O_2$ max. are concerned. Even though they are 2 separate groups, they show a continous spectrum of response. Thus the analysis of all 47 subjects was made first, then of the 2 separate groups. All correlations are made by least squares regression.

(overall results, Table 2-1)

Responsiveness to CO_2.

In the 47 subjects, the range of ventilatory response to CO_2 was from 1.08 to 4.84 litres min^{-1} $mmHg.^{-1}$, (mean 2.61, SD 0.91 SE 0.13). This is comparable with results as given in Section 1A.

The 47 subjects were made up of 10 trained and 37 untrained subjects. In the untrained, the range was from 1.07 to 4.48 litres min^{-1} $mmHg.^{-1}$, (mean 2.88, SD 0.82 SE 0.13). The range and mean in the untrained is similar to reported results for normals (Section 1A) and in the trained slightly higher than found in athletes studied by Byrne-Quinn et al 1971 (mean 0.94 SE 0.08). In this study however, there is a significantly lower "S" in the trained when compared with the untrained ($p<0.001$).

When responsiveness to CO_2 was measured in 16 untrained subjects in terms of maximum rate of mouth occlusion pressure, $\Delta(dp/dt)_{max.} / \Delta PCO_2$, the range was from 1.01 to

Table 2-I. Units used.

$\Delta V_E / \Delta PCO_2$	or 'S'	- ventilatory response to CO_2. (litres min^{-I} $mmHg^{-I}$)
	'B'	- intercept on x axis of ventilatory response to CO_2 slope (mmHg)
$\Delta V_E / \Delta VCO_2$		- ventilatory response to exercise when exercise is expressed as CO_2 produced. litres min^{-I}(litres CO_2
$\Delta V_E / \Delta VO_2$		- ventilatory response to exercise when exercise is expressed as oxygen uptake. litres min^{-I}(litres O_2 min^{-I})$^{-I}$
$\frac{S}{\text{vital capacity}}$		- ventilatory response to CO_2 expressed as fraction of vital capacity . fraction VC/min/mm Hg PCO_2

Table 2-I. Subjects I to 37: Untrained. Table showing data from hypercapnia and exercise tests for all 47 subjects.

Subjects		Age (yrs.)	Hypercapnic Ventilatory response		Ventilatory Response to Exercise		Vital Capacity (Litres)	S / Vital Capacity
			S	B	ΔVE/ΔVO2	ΔVE/ΔVCO2		
1.	GJ	21	4.14	33.84	33.44	38.03	4.6	0.900
2.	ZS	24	4.05	40.68	29.04	27.55	4.7	0.862
3.	RD	22	3.84	38.43	29.70	32.10	6.0	0.641
4.	GM	23	3.67	36.57	31.45	33.34	5.5	0.667
5.	GMD	23	2.42	38.01	24.85	25.20	5.4	0.448
6.	GB	25	4.04.	36.43	30.30	29.70	5.1	0.792
7.	DB	24	2.32	43.95	24.14	26.12	6.0	0.386
8.	SC	23	3.02	41.82	37.57	29.46	3.6	0.839
9.	PC	24	2.15	36.51	21.77	24.43	6.3	0.341
10.	DS	26	2.66	40.15	31.11	28.80	4.2	0.634
11.	JM	25	3.80	37.32	27.35	27.20	5.8	0.655
12.	TM	23	2.12	41.91	25.37	23.84	4.2	0.505
13.	JF	23	2.97	42.14	24.87	26.17	6.0	0.495
14.	KM	22	2.53	36.71	28.31	27.30	5.8	0.436
15.	DI	23	3.55	42.78	30.86	26.77	6.8	0.520
16.	JK	21	2.43	36.66	24.33	26.15	5.5	0.442

Table 2-1 (contd)

	Subjects	Age (yrs.)	Hypercapnic Ventilatory response		Ventilatory Response to Exercise		Vital Capacity (Litres)	S / Vital Capacity
			S	B	ΔVE/ΔVO2	ΔVE/ΔVCO2		
17.	PP	24	3.70	43.17	30.30	29.00	6.0	0.617
18.	IP	26	3.81	48.71	38.82	35.89	4.1	0.925
19.	KG	23	2.61	38.23	24.44	20.67	6.2	0.421
20.	AZ	25	2.50	36.38	27.35	29.52	3.4	0.735
21.	VE	25	3.12	42.62	26.22	31.74	5.5	0.566
22.	PK	24	2.79	37.81	24.10	29.00	4.9	0.569
23.	BP	21	3.45	36.20	30.05	28.50	4.8	0.719
24.	FMG	26	2.38	43.95	25.01	27.80	6.0	0.397
25.	RN	26	1.40	38.00	19.70	21.30	6.5	0.215
26.	YM	25	3.55	42.88	28.75	30.73	4.1	0.866
27.	NS	24	2.36	47.74	26.05	28.87	3.5	0.674
28.	MS	23	2.15	37.43	24.47	23.84	5.5	0.391
29.	DMI	25	1.53	35.56	24.62	25.29	6.3	0.242
30.	HS	25	2.67	37.87	24.55	25.11	5.5	0.485

Table 2-1 (contd)

Subjects	Age (yrs.)	Hypercapnic Ventilatory response		Ventilatory Response to Exercise		Vital Capacity (Litres)	S / Vital Capacity
		S	B	ΔVE/ΔVO2	ΔVE/ΔVCO2		
31. FH	26	1.97	46.76	26.44	25.42	3.2	0.616
32. KL	27	1.07	35.16	17.85	18.38	4.4	0.244
33. DW	22	2.22	39.12	28.00	27.53	6.0	0.370
34. BB	25	3.15	45.80	25.34	28.06	5.0	0.624
35. GML	24	2.82	40.22	25.10	27.73	4.6	0.612
36. KH	24	3.13	38.67	28.10	30.75	4.7	0.665
37. GD	26	4.48	45.69	35.60	29.07	4.2	1.066
Untrained							
Mean	24.00	2.88	40.13	27.44	27.73	5.1	0.583
S.D.	1.56	0.82	3.73	4.40	3.83	0.95	0.20
S.E.	0.25	0.13	0.61	1.39	0.63	0.15	0.03

Table 2-I (contd) Subjects 38 to 47: Trained.

Subjects		Age (yrs.)	Hypercapnic Ventilatory response		Ventilatory Response to Exercise		Vital Capacity (Litres)	S / Vital Capacity
			S	B	ΔVE/ΔVO2	ΔVE/ΔVCO2		
38.	SM	25	1.43	37.53	20.19	18.74	4.8	0.299
39.	JI	26	2.08	38.73	28.81	26.15	5.4	0.385
40.	AH	24	1.11	40.32	20.00	17.38	6.0	0.185
41.	NR	24	1.57	39.86	24.50	23.86	4.5	0.350
42.	DR	24	1.54	42.98	18.84	18.87	5.9	0.264
43.	SJ	26	1.26	40.18	19.18	19.05	4.0	0.315
44.	AT	22	1.85	38.18	26.76	28.56	4.5	0.412
45.	GD	22	1.93	41.55	28.30	24.70	5.6	0.345
46.	SG	23	1.92	41.89	23.10	21.88	4.8	0.395
47.	GRM	24	1.18	43.09	15.59	19.29	5.3	0.224
Trained								
	Mean	24.00	1.59	40.43	22.56	21.83	5.1	0.317
	S.D.	1.41	0.34	1.93	4.40	3.79	0.66	0.07
	S.E.	0.44	0.11	0.61	1.39	1.20	0.21	0.02
Trained and Untrained								
	Mean	24.00	2.61	40.25	26.40	26.48	5.1	0.527
	S.D.	1.52	0.91	3.48	4.80	4.50	0.89	0.21
	S.E.	0.22	0.13	0.50	0.70	0.66	0.13	0.03

3.73 cm.H_2O sec^{-1} mmHg.CO_2^{-1} (mean 2.59 SD 0.82 SE 0.20) which is comparable to findings in Section 1A and Matthews and Howells' 1975 (see Section 1A).

Response to hypoxia at rest.

11 subjects were studied to find their response to isocapnic hypoxia at rest. As described in Section 1A, the hypoxia response was measured in 2 ways, parameter "A" and parameter "A $(dp/dt)_{max.}$".

In terms of parameter 'A', the range was from 86.62 to 219.51 (mean 156.39 SD 45.51 SE 13.72). It is within range of values found by different investigators (see Section 1A). In terms of parameter '$A\ (dp/dt)_{max.}$', the values obtained range from 84.66 to 252.97 (mean 163.59 SD 57.09 SE 17.21).

Ventilatory response to exercise (linear portion of slopes, $\triangle \dot{V}_E / \triangle \dot{V}O_2$ and $\triangle \dot{V}_E / \triangle \dot{V}CO_2$).

In the 47 subjects, when exercise is expressed in terms of O_2 uptake, the range was from 15.96 to 38.82 litres min^{-1} (litres O_2 min^{-1} $)^{-1}$, (mean 26.40 SD 4.80 SE 0.70). This is comparable to values reported previously, as shown overleaf.

Workers	Sample size	mean value. $\Delta\dot{V}_E / \Delta\dot{V}O_2$ L min^{-1} $(L.O_2 min^{-1})^{-1}$
Cunningham 1963	values quoted from different tests in literature.	23.50
Rebuck et al 1973	11	29.02
Present study	47	26.40

In the 37 untrained subjects, the range was from 17.85 to 38.82 litres min^{-1} (Litres O_2 min^{-1} $)^{-1}$, (mean 27.44 SD 4.40 SE 0.72). In the trained subjects there is a significantly lower ventilatory response to exercise, ($p<0.01$) with range from 1.11 to 2.08 litres min^{-1} (Litres O_2 min^{-1} $)^{-1}$, (mean 22.56 SD 4.40 SE 1.39).

When exercise is expressed in terms of CO_2 produced, the range in the 47 subjects was from 17.38 to 38.03 litres min^{-1} (Litres CO_2 min^{-1} $)^{-1}$, (mean 26.48 SD 4.50 SE 0.65), which is comparable to Rebuck et al 1973 findings, (range 16.6 to 32.0, mean 22.7 SD 5.35). In the untrained the figures obtained respectively are 18.38 to 38.02 (mean 27.7 SD 3.83 SE 0.63) and in the trained 17.38 to 28.56 (mean 21.83 SD 3.79 SE 1.20). There is a significantly lower response in the trained compared to the untrained ($p< 0.001$).

Repeats on exercise ventilatory response test.

Results on repeat tests done by 5 untrained and 1 trained subjects on the exercise ventilatory response is as follows.

Subjects	$\Delta \dot{V}_E / \Delta \dot{V}O_2$		$\Delta \dot{V}_E / \Delta \dot{V}CO_2$	
	$L.min^{-1} (L.O_2 min^{-1})^{-1}$		$L.\ min^{-1} (L.CO_2 min^{-1})^{-1}$	
	1st.	2nd.	1st.	2nd.
1. GJ	33.34	30.37	38.03	36.77
7. DB	24.14	25.69	26.12	28.54
21. VE	26.22	27.34	31.74	29.12
27. NS	26.05	27.13	28.87	27.67
30. HS	24.55	25.66	25.11	27.14
43. SJ	19.18	16.81	18.30	15.75

The variation between the first and second tests was small and similar for both the exercise ventilatory response.

Correlation between CO_2 responsiveness and ventilatory response to exercise.

a) $\Delta \dot{V}_E / \Delta PCO_2$ and $\Delta \dot{V}_E / \Delta \dot{V}O_2$.

In the 47 subjects, a significant correlation between CO_2 response ($\Delta \dot{V}_E / \Delta PCO_2$) and exercise response, when exercise is exp-

ressed as O_2 uptake, (Fig. 2-1), r= 0.788 p=< 0.001 was found.

The same significant relationship was obtained in both untrained (r= 0.750 p= < 0.001) and trained (r= 0.868 p= < 0.01) subjects. (Fig. 2-2).

Even though there is no correlation between lung size as expressed by vital capacity , and CO_2 responsiveness, the 'S' was 'corrected' for lung size to see if any correlation between 'corrected' 'S' and exercise response still exists.

In the 47 subjects, when 'S' is corrected for lung size, there is still a highly significant correlation between 'corrected' S and exercise response.(r= 0.739 p= < 0.001) (Fig. 2-3). Significant correlations were found for the untrained (r= 0.812 p= < 0.001) and the trained (r= 0.769 p= < 0.01) (Fig. 2-4)

b) $\triangle(dp/dt)_{max.} / \triangle PCO_2$ and $\triangle \dot{V}_E / \triangle \dot{V}O_2$.

In the 16 untrained subjects, the $(dp/dt)_{max.}$ response to CO_2 shows a significant correlation with exercise response (r= 0.818 p=<0.001) (Fig. 2-5a). (The same 16 subjects showed similar significant relationship when CO_2 response expressed as $\triangle \dot{V}_E / \triangle PCO_2$, r= 0.759 p=<0.001; Fig. 2-5b)

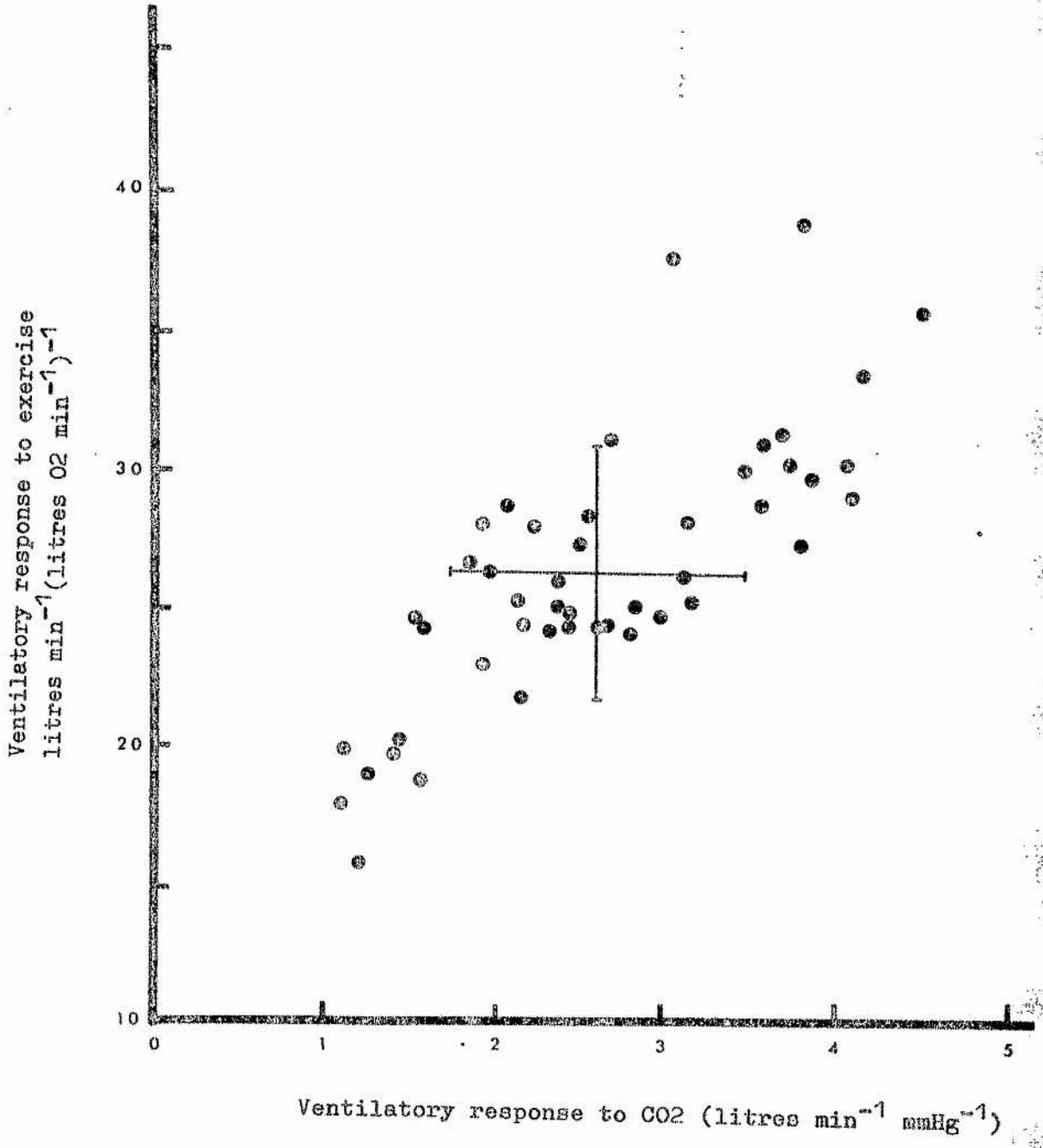


Fig. 2-1. Change in ventilation per litre of O2 uptake during exercise, plotted against the ventilatory response to CO2 at rest. Each dot represents one subject. All 47 subjects are recorded here, bars show mean and S.D. for each of these measurements. r= 0.788 $p = < 0.001$.

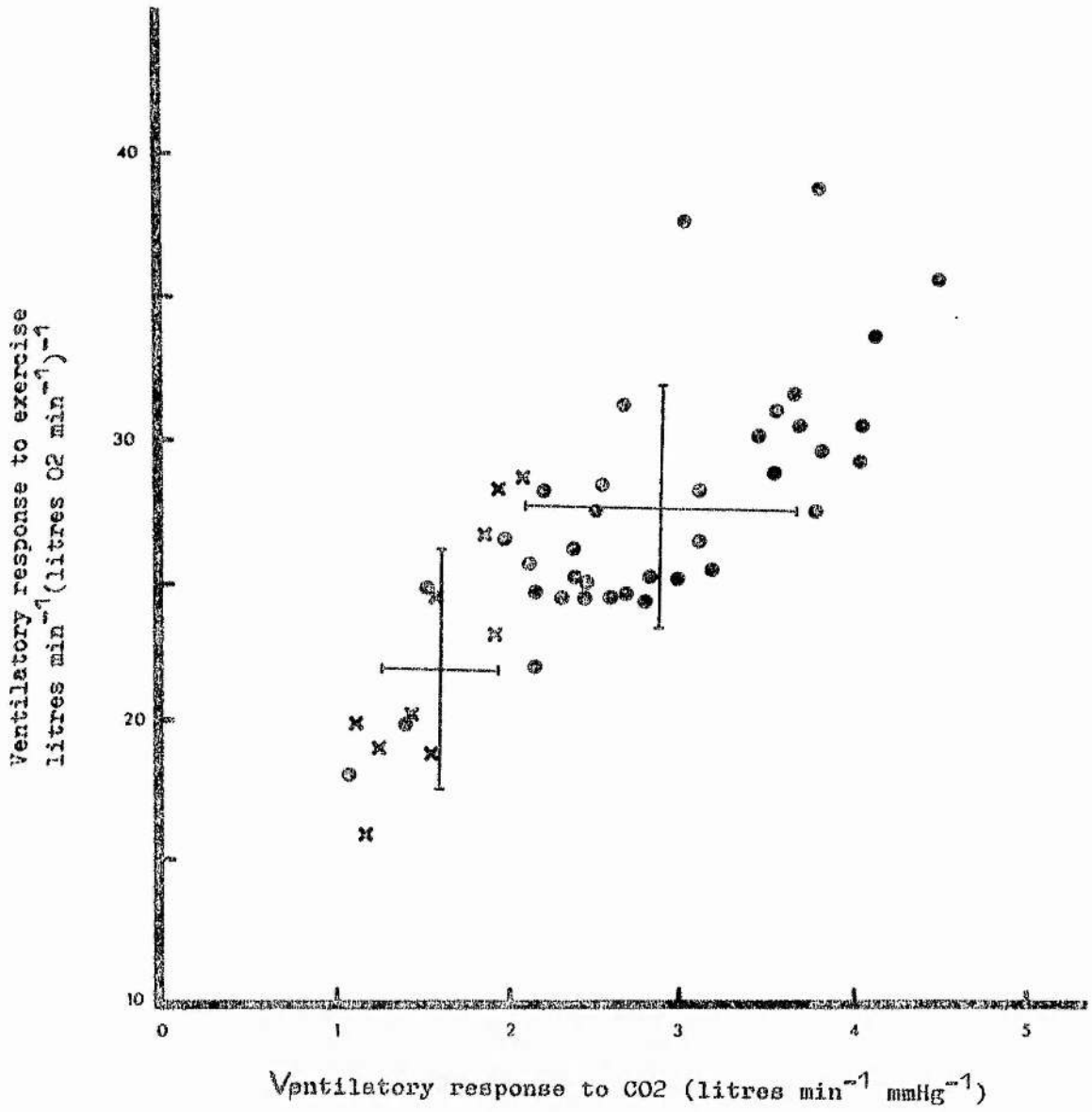


Fig. 2-2. Change in ventilation per litre of O2 uptake during exercise, plotted against the ventilatory response to CO2 at rest. Each point represents one subject, (● untrained, ✖ trained), bars show mean and S.D. for each of the 2 groups of subjects.
untrained r= 0.751 p= < 0.001
trained r= 0.869 p= < 0.01

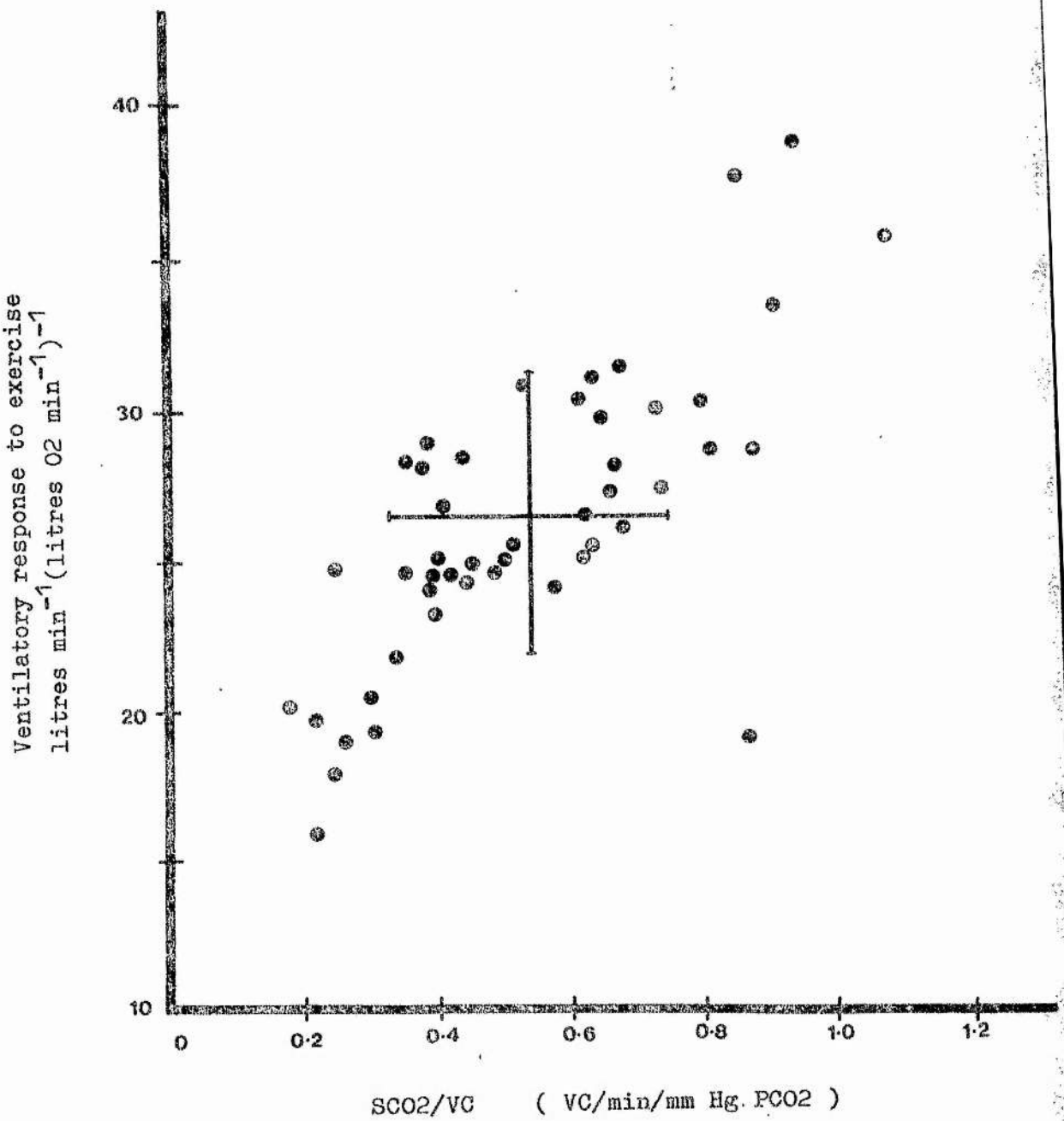


Fig. 2-3. Change in ventilation per litre of O2 uptake during exercise, plotted against the ventilatory response to CO2 "corrected for lung size", at rest. Each dot represents one subject. All 47 subjects are recorded here, bars show mean and S.D. for each of these measurements. $r = 0.739$ $p = < 0.001$.

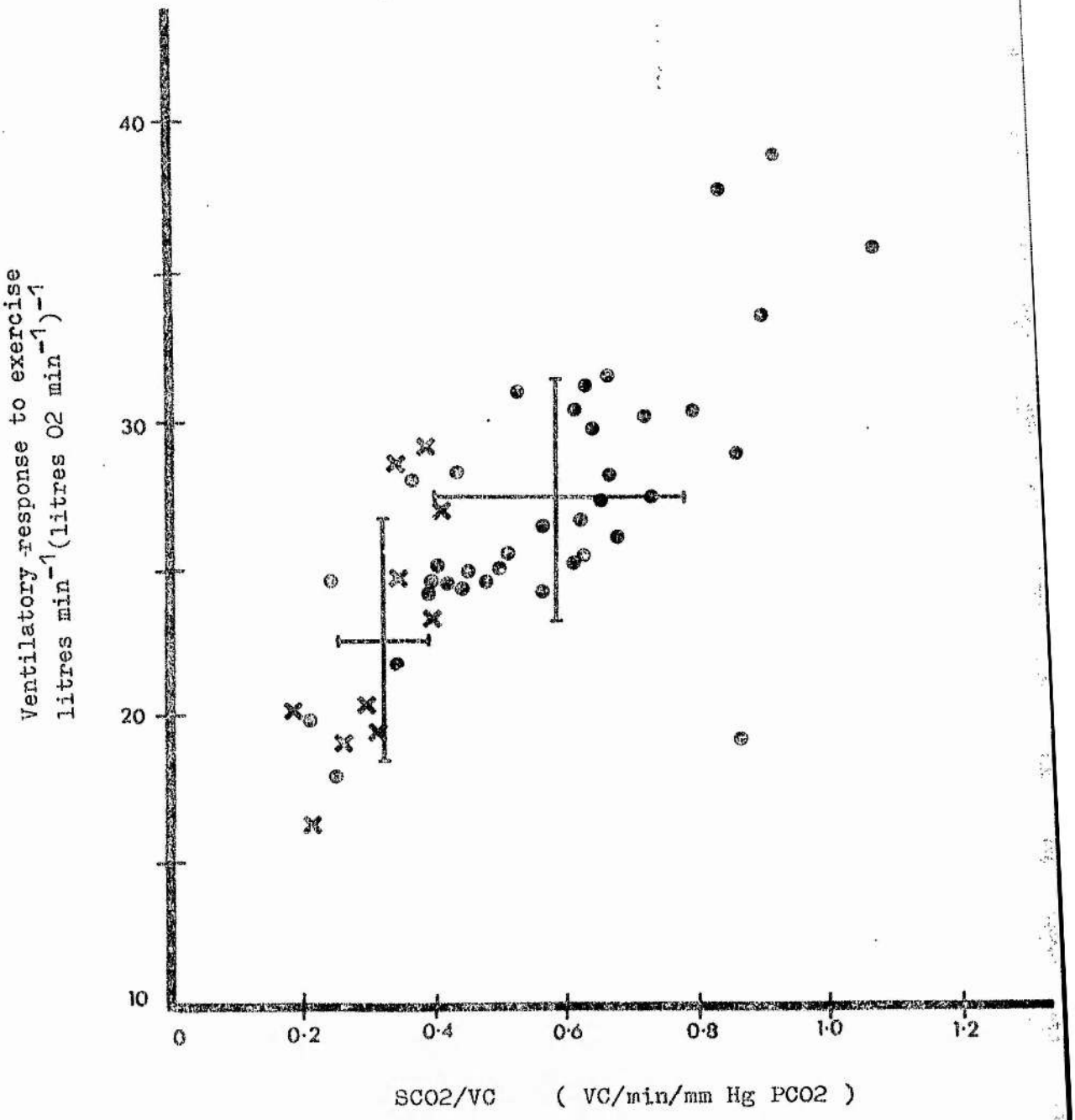


Fig. 2-4. Change in ventilation per litre of O2 uptake during exercise, plotted against the ventilatory response to CO2, "corrected for lung size", at rest. Each point represents one subject. (● untrained ✕ trained), bars show mean and S.D. for each of the 2 groups of subjects.

untrained r= 0.813 $p < 0.001$

trained r= 0.769 $p \ll 0.01$

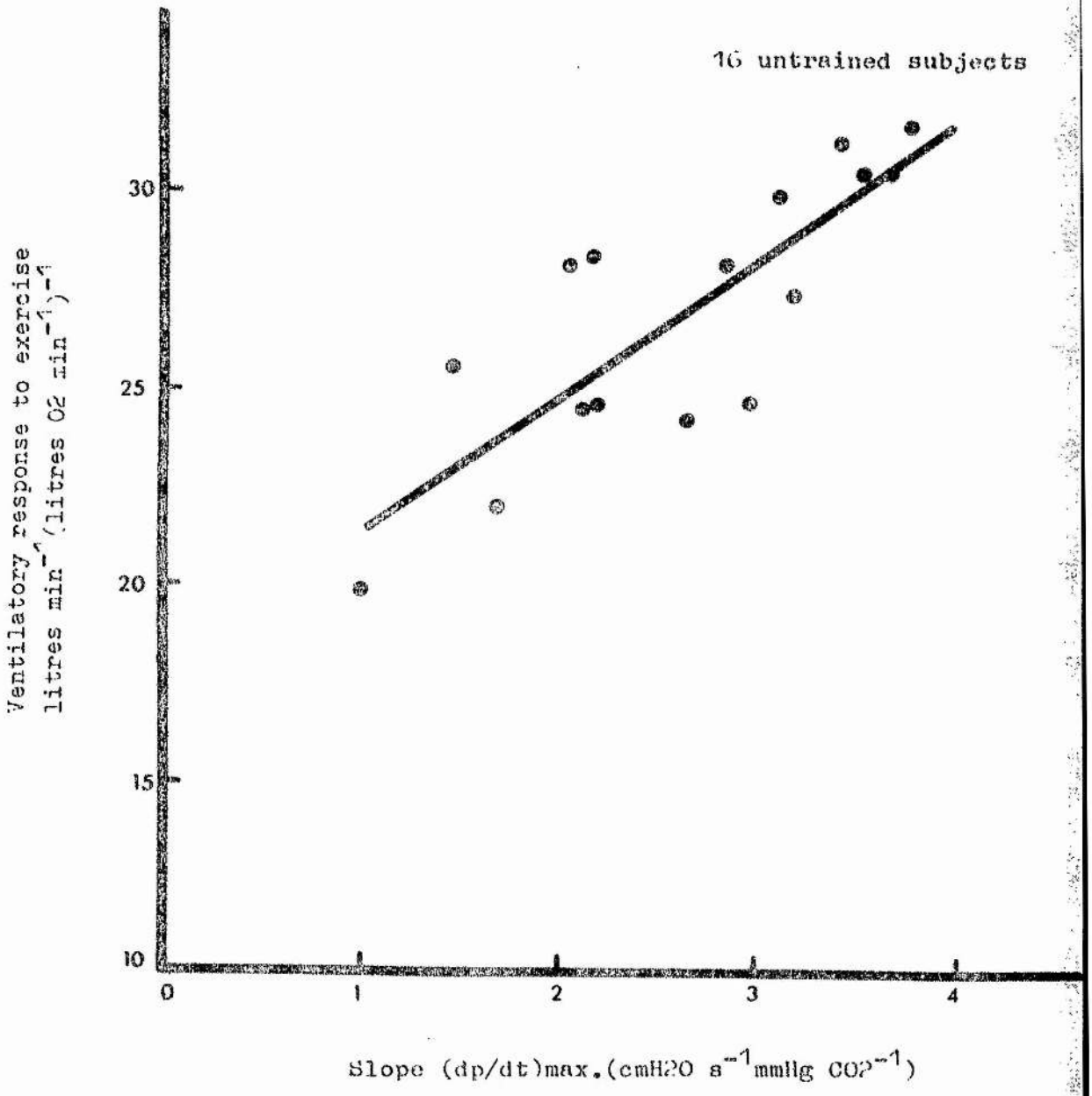


Fig. 2-5a. Correlation of ventilatory response to exercise (when exercise is expressed as O2 uptake) and (dp/dt)max. response to CO2 at rest in 16 subjects.
r= 0.818 p= $<$ 0.001

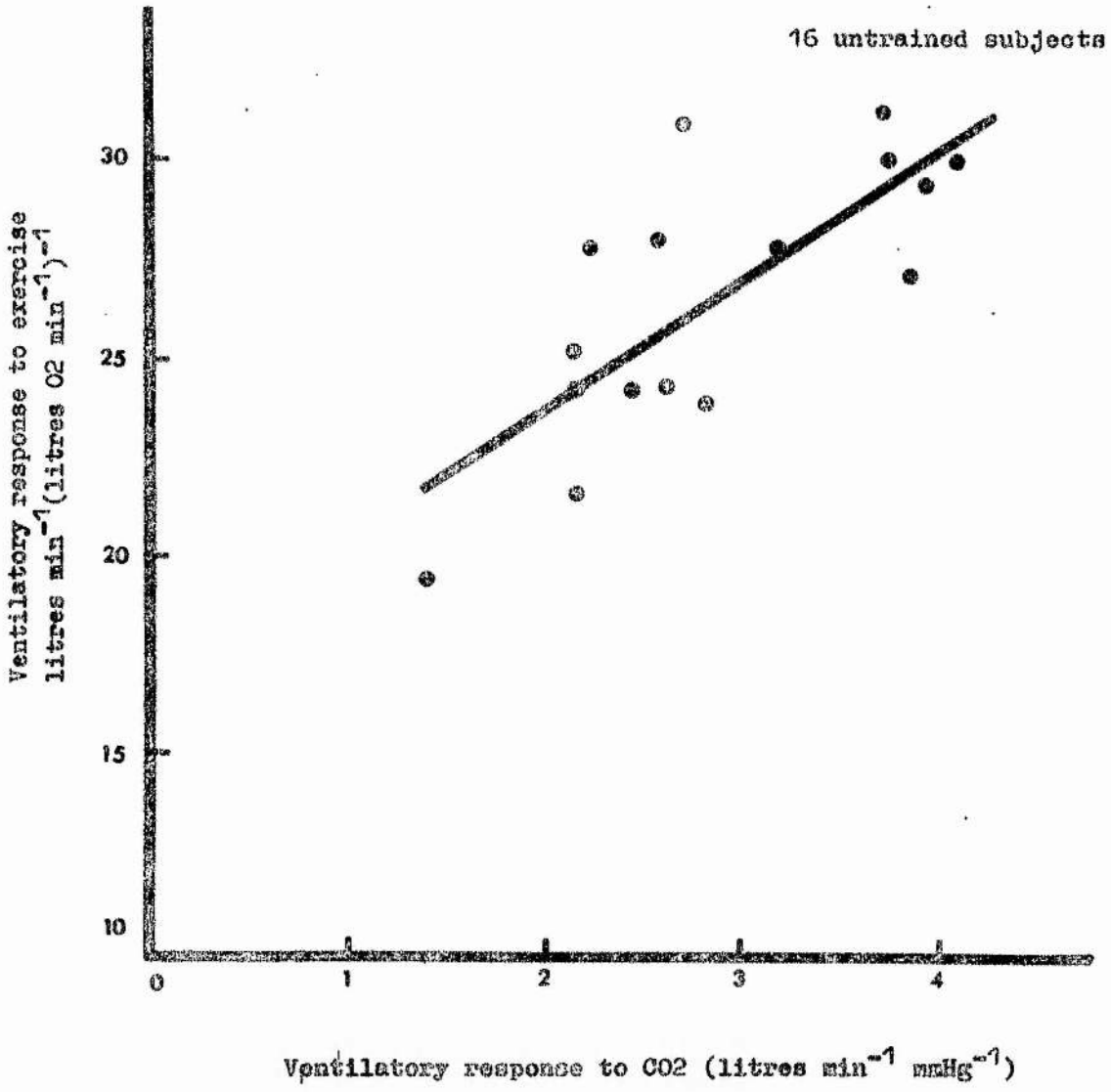


Fig. 2-5b. Correlation of ventilatory response to exercise (when exercise is expressed as O2 uptake) and ventilatory response to CO2 at rest in same 16 subjects as in fig. 2-5a.
r= 0.759 p= <0.001

c) $\Delta\dot{V}_E / \Delta PCO_2$ and $\Delta\dot{V}_E / \Delta\dot{V}CO_2$.

In the 47 subjects, there is a significant correlation between S and exercise response as expressed as CO_2 production. (r= 0.799 p= $<$0.001) (Fig. 2-6). The same significant relationship exists for the untrained (r= 0.721 p= $<$0.001) and the trained (r= 0.819 p=$<$0.01) (Fig. 2-7).

After 'correction' for lung size, the significant relationship still exists. Values respectively are :- 47 subjects, r= 0.791 p= $<$ 0.001 (Fig. 2-8a), untrained r= 0.730 p= $<$ 0.001 and trained r= 0.834 p= $<$ 0.01 (Fig. 2-8b).

d) $\Delta(dp/dt)_{max.} / \Delta PCO_2$ and $\Delta\dot{V}_E / \Delta\dot{V}CO_2$.

When expressed in terms of $(dp/dt)_{max.}$, the responsiveness to CO_2 in the 16 subjects shows a significant correlation with the exercise response (r= 0.742 p= $<$0.001) (Fig. 2-9a). (The same 16 subjects show similar significant relationship when CO_2 responsiveness is expressed as $\Delta\dot{V}_E / \Delta PCO_2$ r= 0.752 p= $<$0.001.(Fig. 2-9b).

The findings here of significant correlation between ventilatory response to CO_2 and exercise ventilatory response are similar to findings by Rebuck et al 1972.

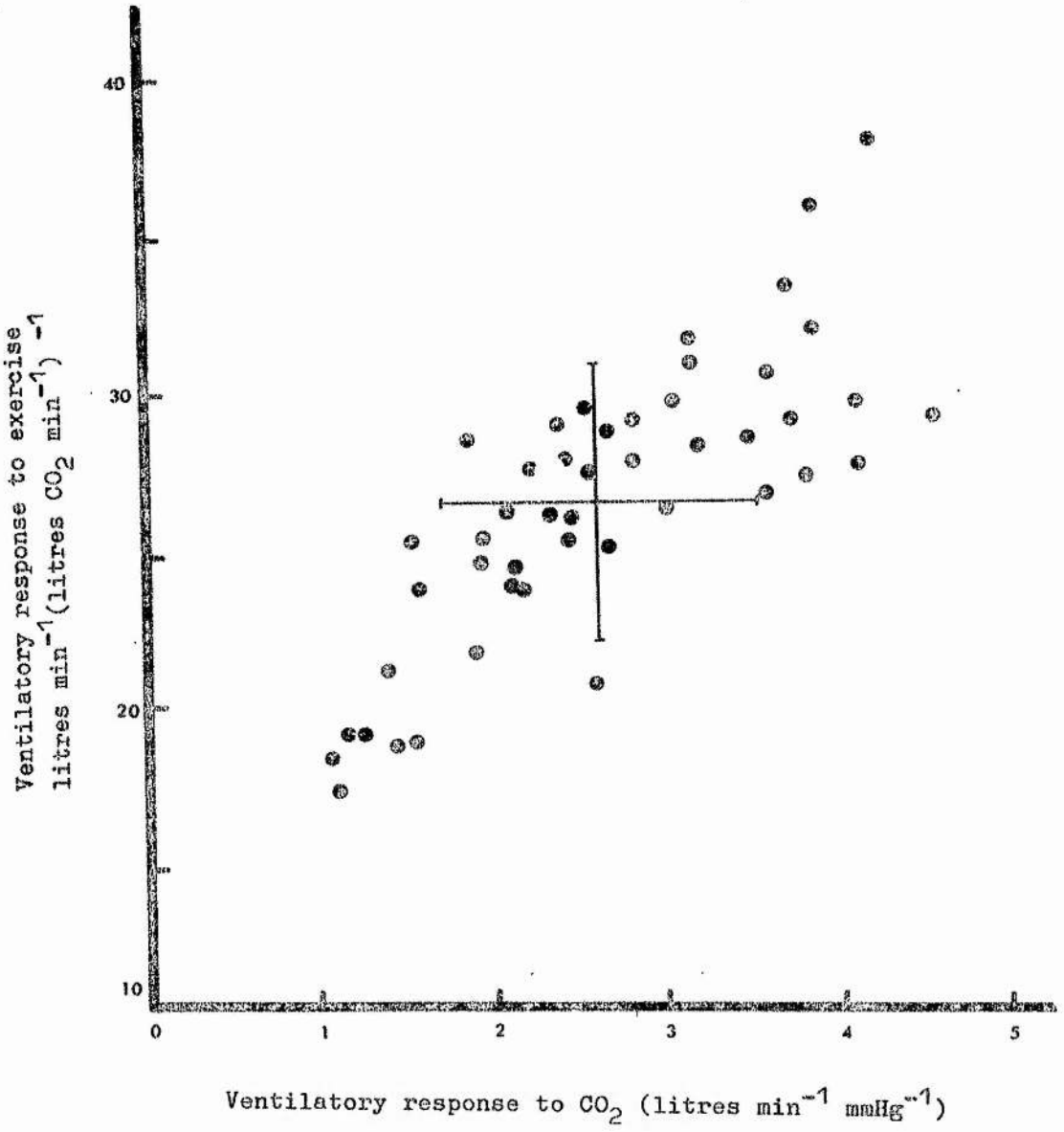


Fig. 2-6. Change in ventilation per litre of CO2 production during exercise, plotted against the ventilatory response to CO2 at rest. Each dot represents one subject. All 47 subjects are recorded here, bars show mean and S.D. for each of these measurements. r= 0.799 p=<0.001.

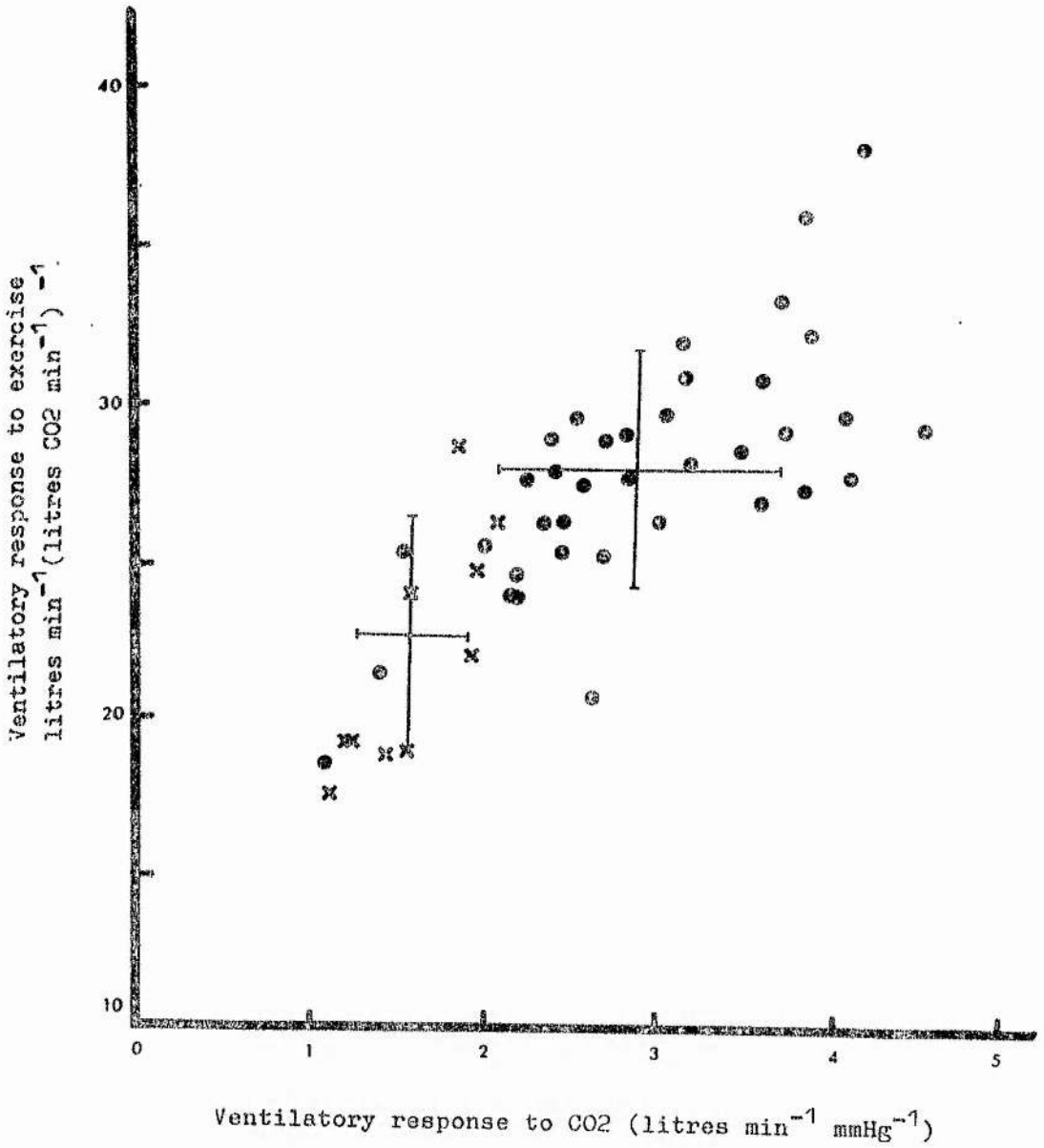


Fig. 2-7. Change in ventilation per litre of CO2 production during exercise, plotted against the ventilatory response to CO2 at rest. Each point represents one subject, (⊛ untrained, ✖ trained), bars show mean and S.D. for each of the 2 groups of subjects. untrained $r = 0.722$ $p < 0.001$
trained $r = 0.819$ $p < 0.01$

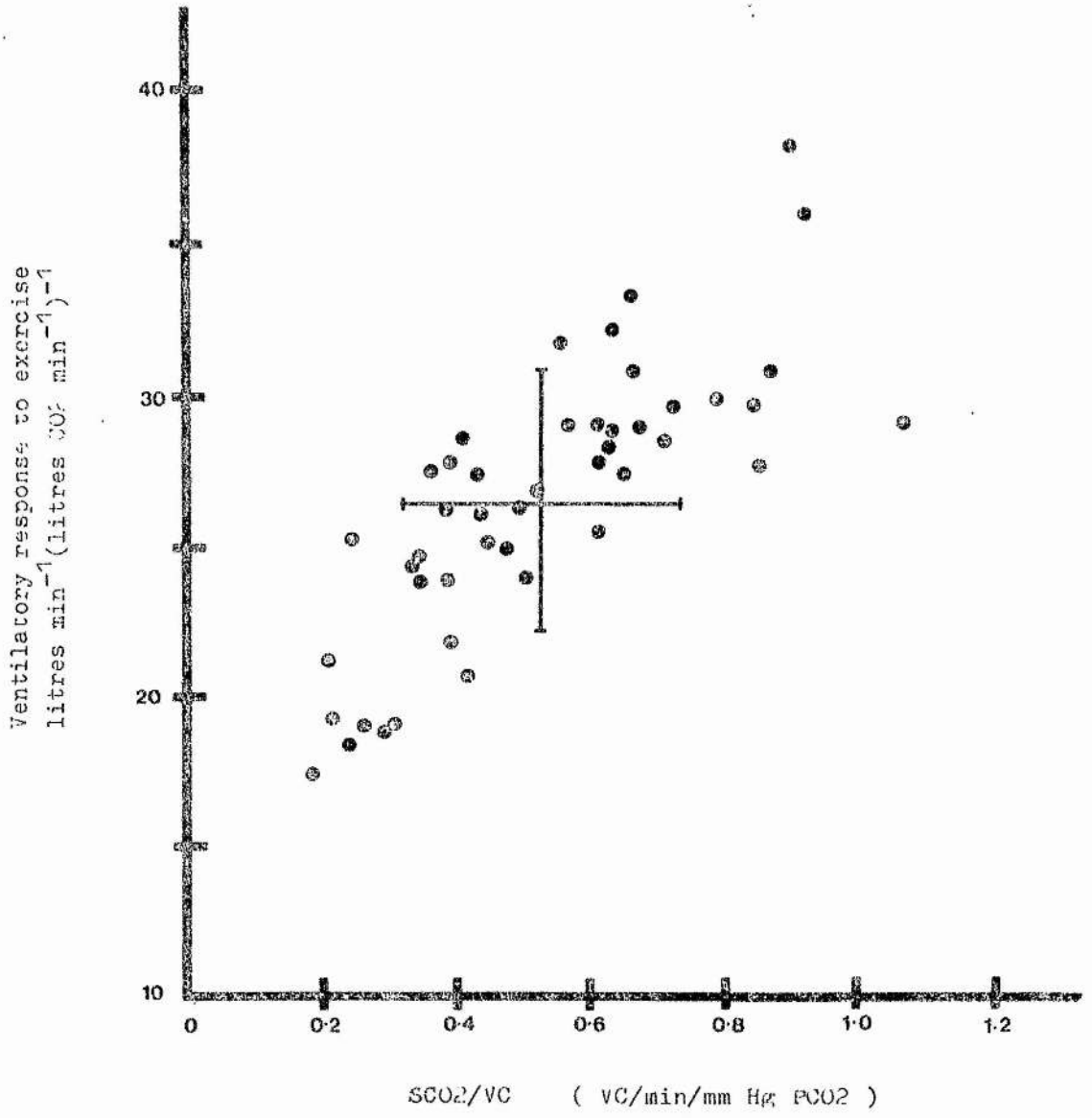


Fig. 2-8. Change in ventilation per litre of CO_2 production during exercise, plotted against the ventilatory response to CO_2 "corrected for lung size", at rest. each dot represents one subject. All 47 subjects are recorded here, bars show mean and S.D. for each of these measurements. $r = 0.701$ $p < 0.001$.

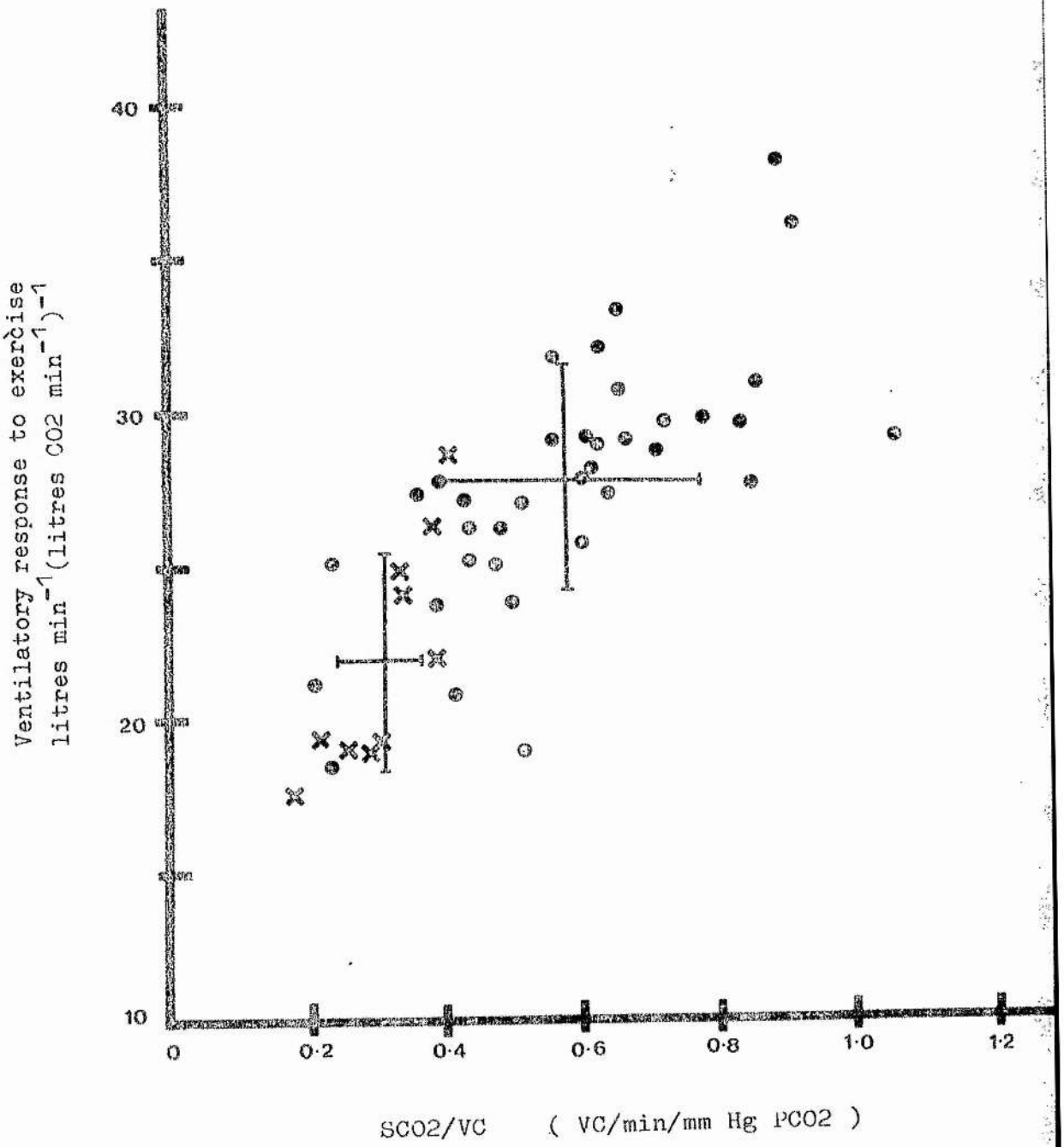


Fig. 2-8b. Change in ventilation per litre of CO2 production during exercise, plotted against the ventilatory response to CO2, "corrected for lung size", at rest. Each point represents one subject. (● untrained ✖ trained), bars show mean and S.D. for each of the 2 groups of subjects.

untrained r= 0.730 p=<0.001

trained r= 0.834 p=<0.01

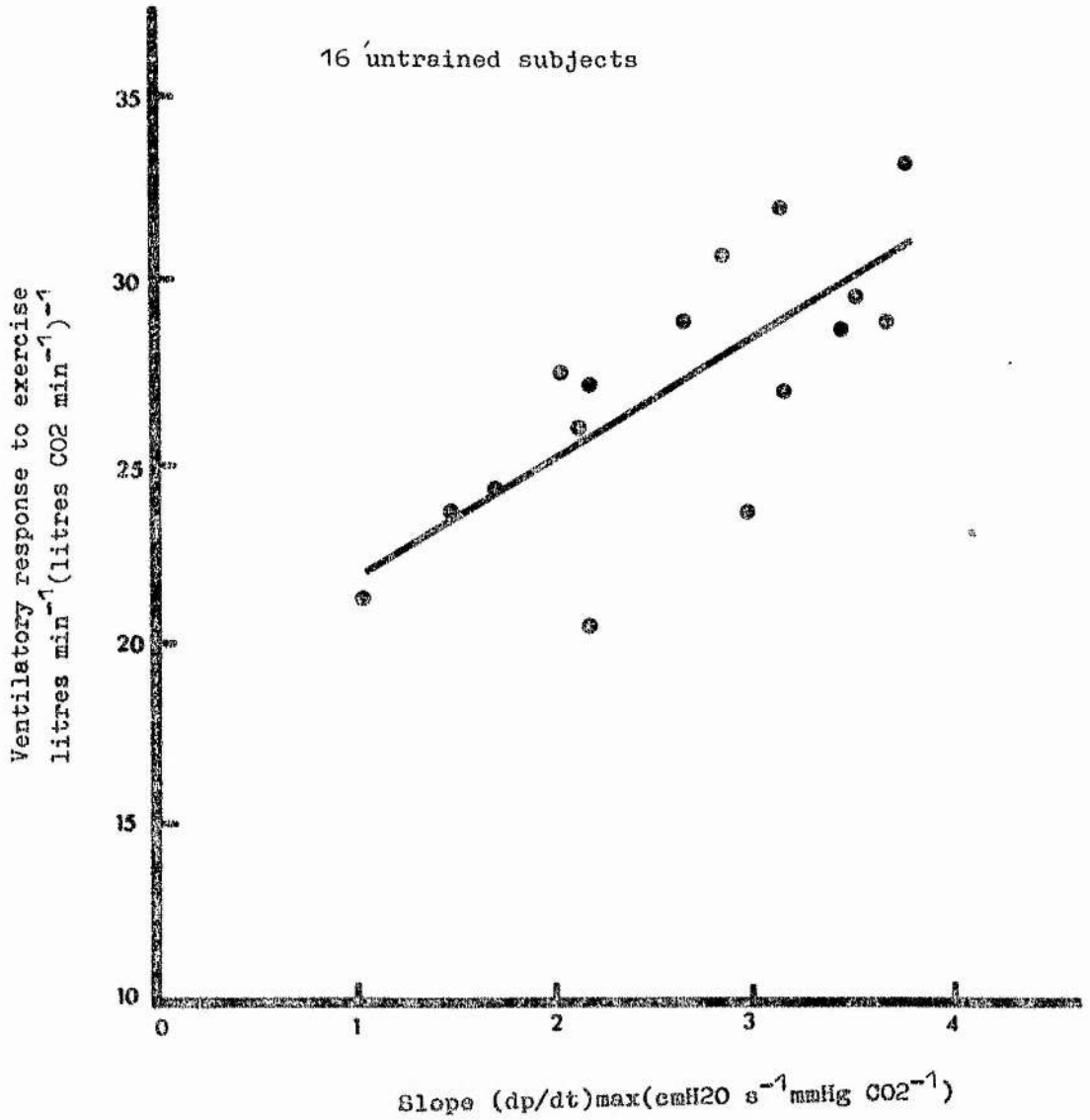


Fig. 2-9a. Correlation of ventilatory response to exercise (when exercise is expressed as CO2 production) and (dp/dt)max response to CO2 at rest in 16 subjects.
r= 0.742 p= $<$ 0.001

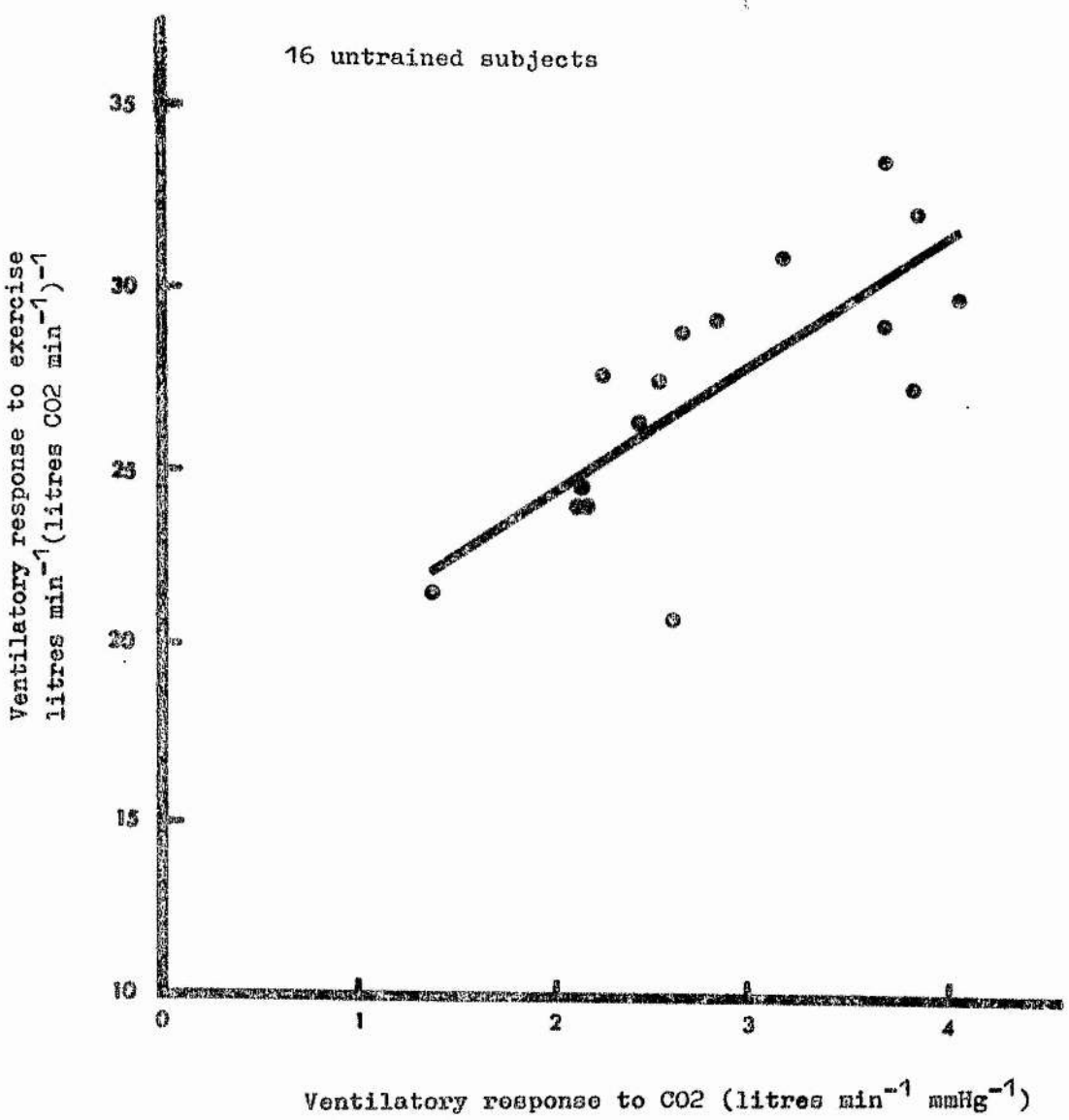


Fig. 2-9b. Correlation of ventilatory response to exercise (when exercise is expressed as CO2 production) and ventilatory response to CO2 at rest in same 16 subjects as in fig. 2-9a.
r= 0.752 p= < 0.001

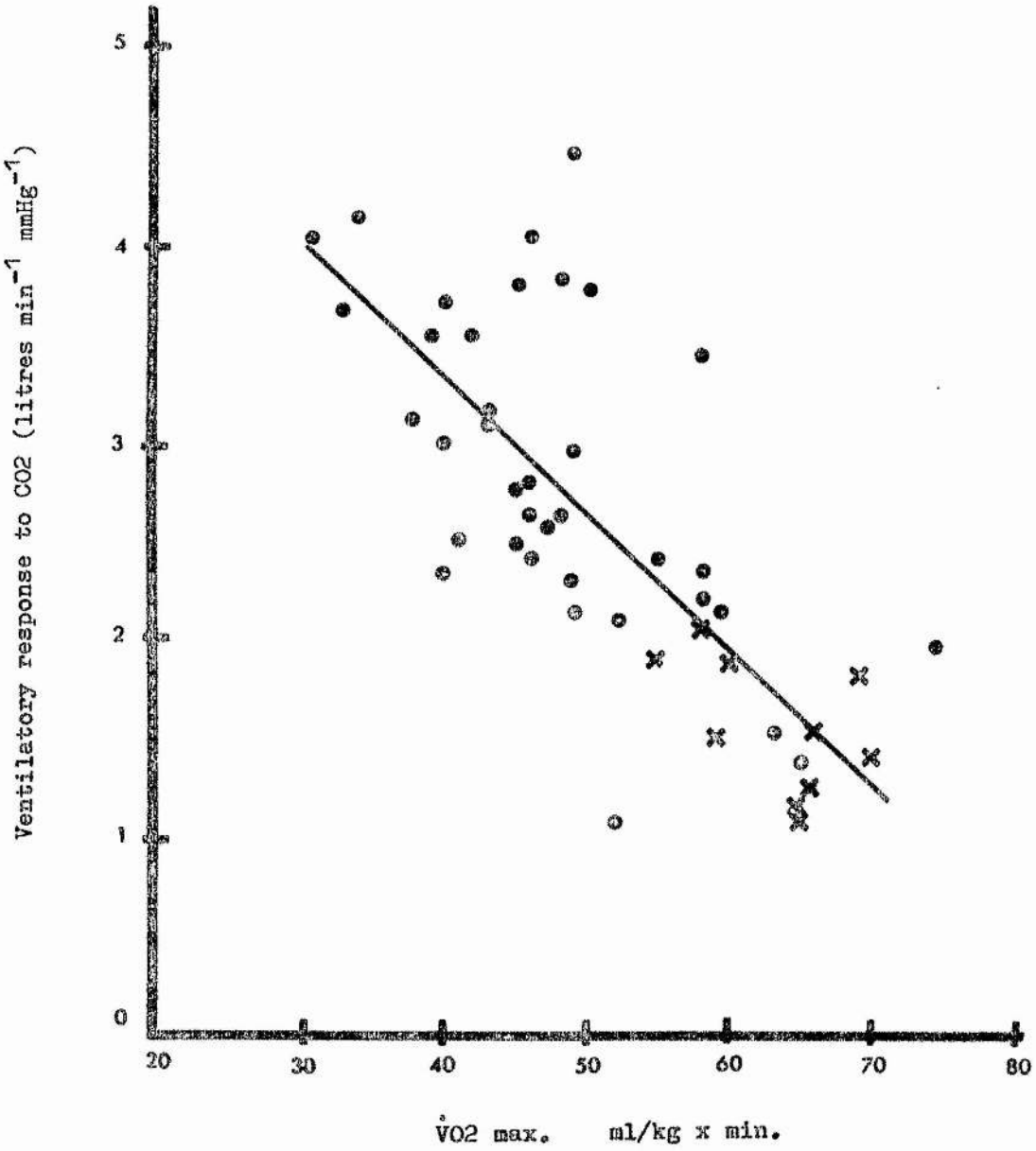


Fig. 2-10a. Correlation between ventilatory response to CO2 and $\dot{V}O_2$ max. in all 47 subjects.(✖ trained ⊙ untrained)
r= - 0.744 p= < 0.001

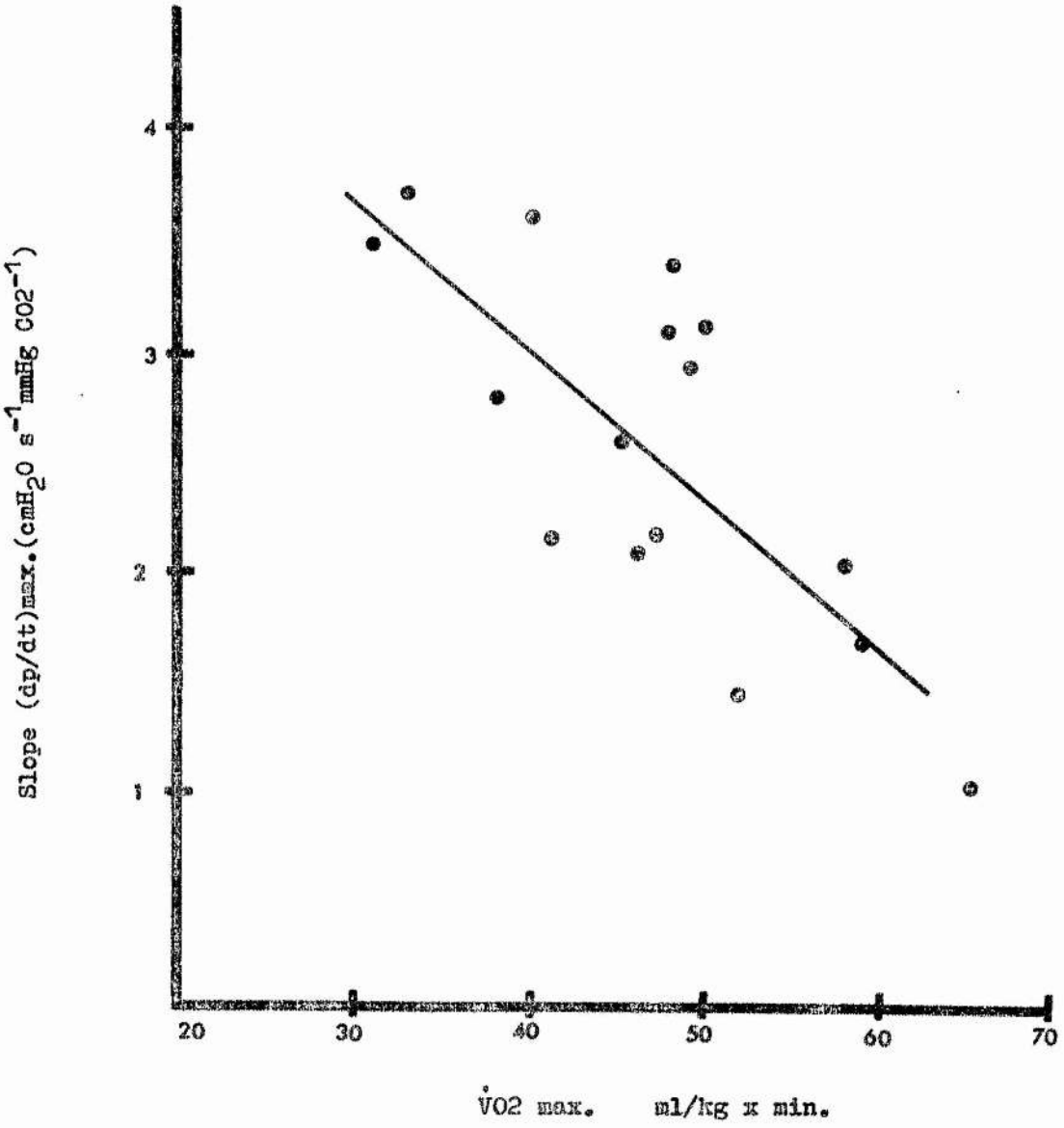


Fig. 2-10b. Correlation between (dp/dt)max. response to CO2 $\dot{V}O_2$ max. in 16 untrained subjects.
r= - 0.747 p= < 0.001

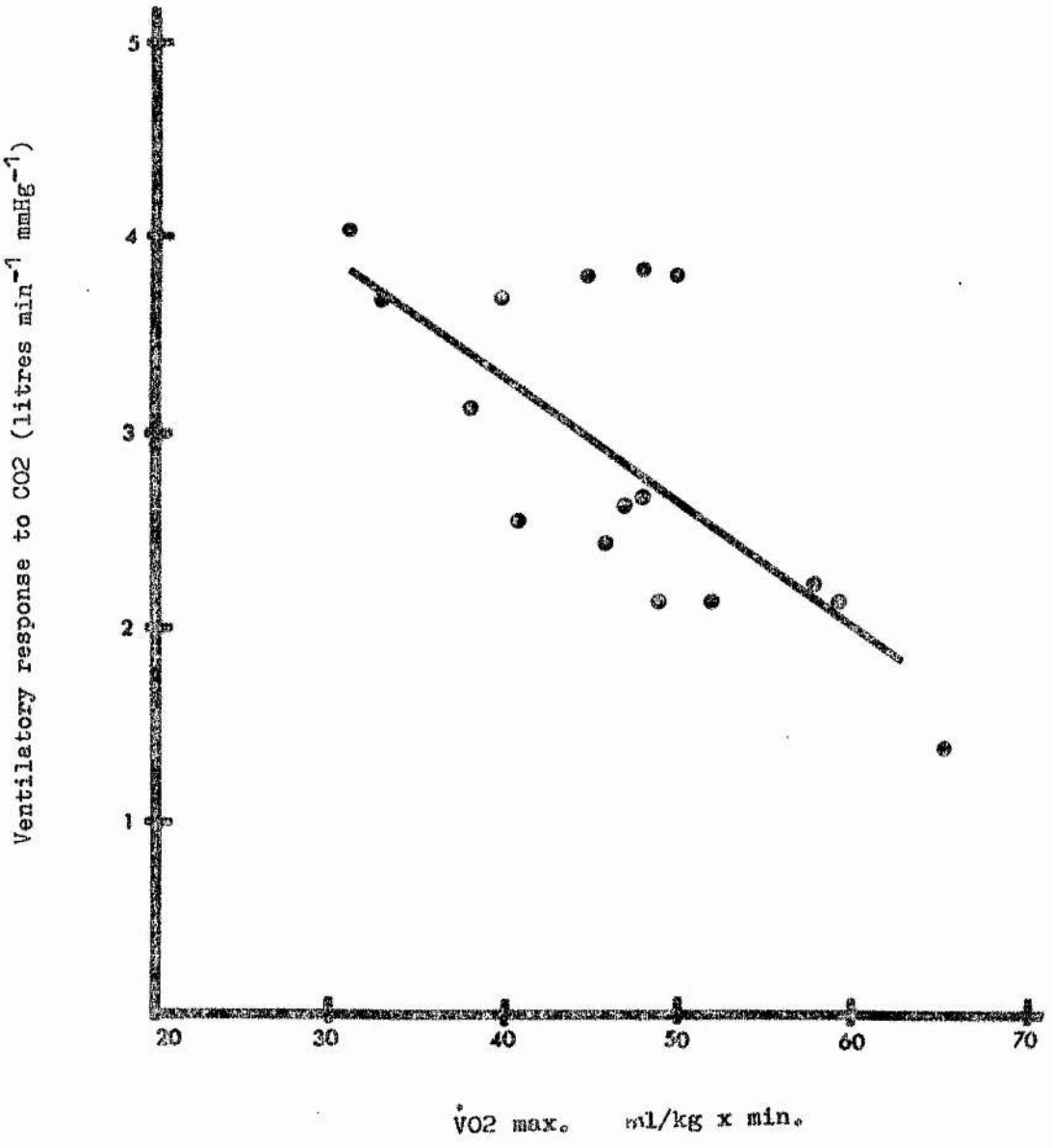


Fig. 2-10c. Correlation between ventilatory response to CO2 and $\dot{V}O_2$ in the same 16 untrained subjects as in fig. 2-10b.
$r = -0.742$ $p < 0.001$

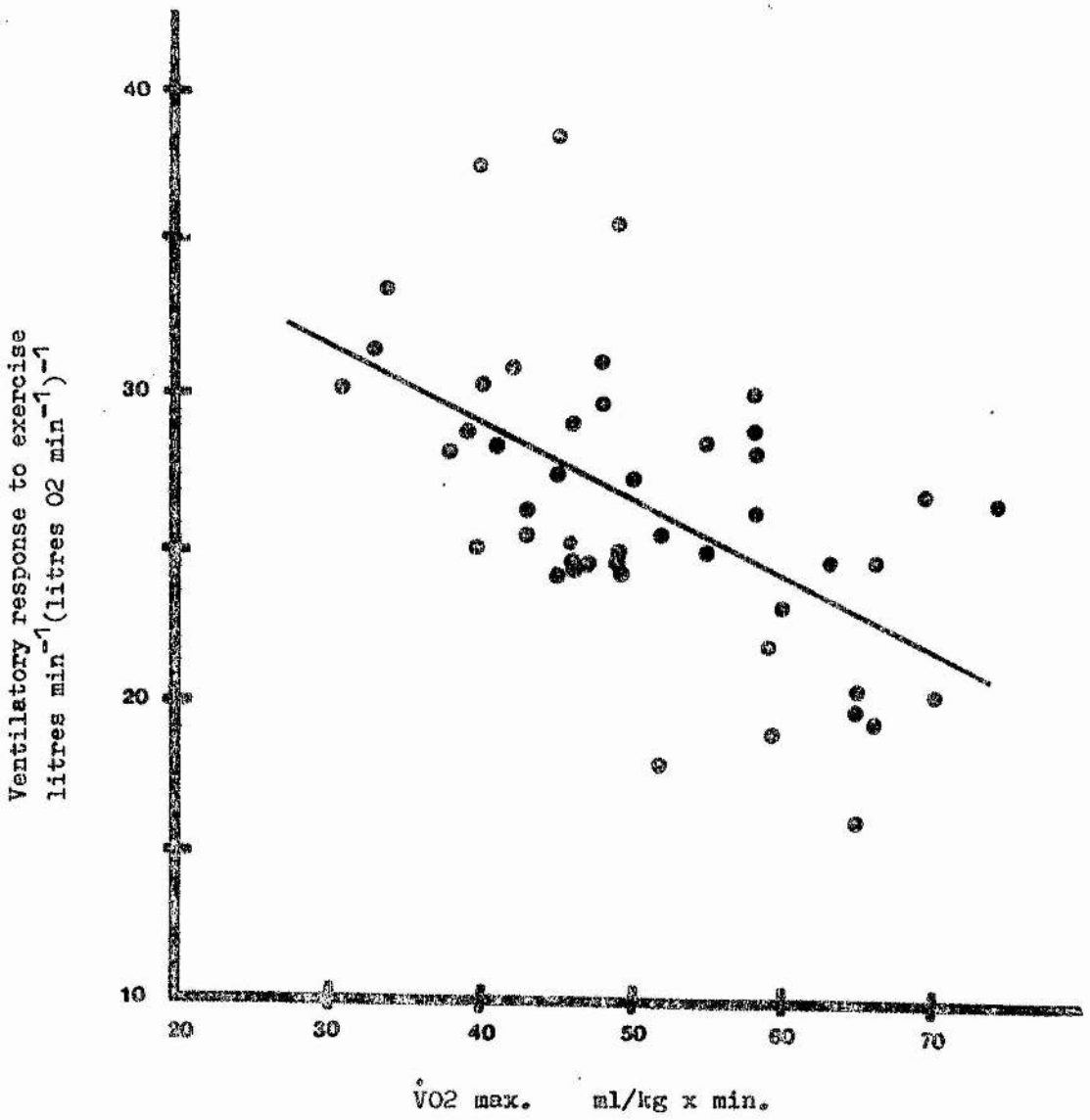


Fig. 2-10d. Correlation between ventilatory response to exercise (when exercise is expressed as 02 uptake) and $\dot{V}$02 max. in all 47 subjects.

r= - 0.560 p= < 0.001

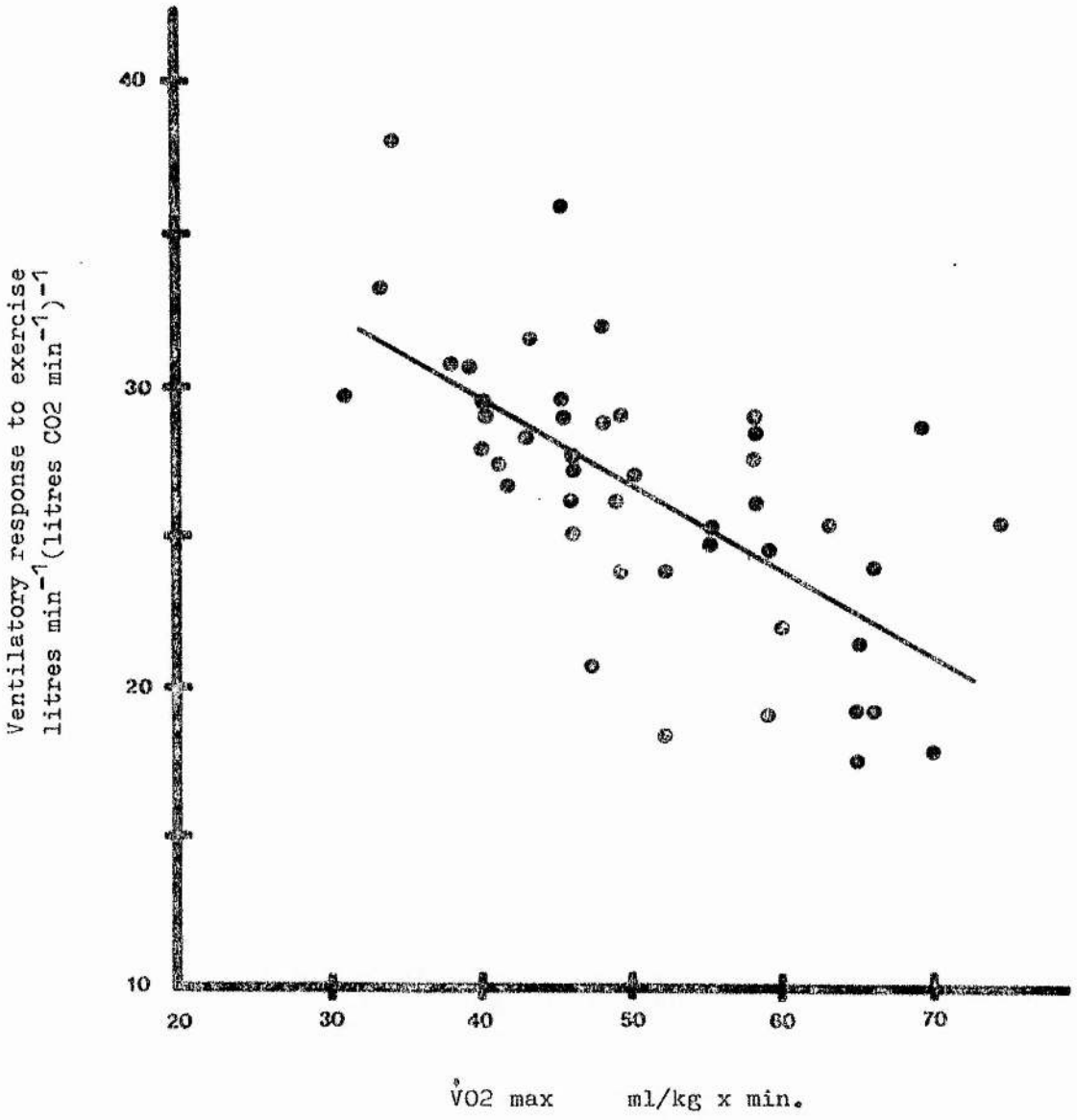


Fig. 2-10e. Correlation between ventilatory response to exercise (when exercise is expressed as CO2 production) and $\dot{V}$O2 max. in all 47 subjects.
r= - 0.660 p= < 0.001

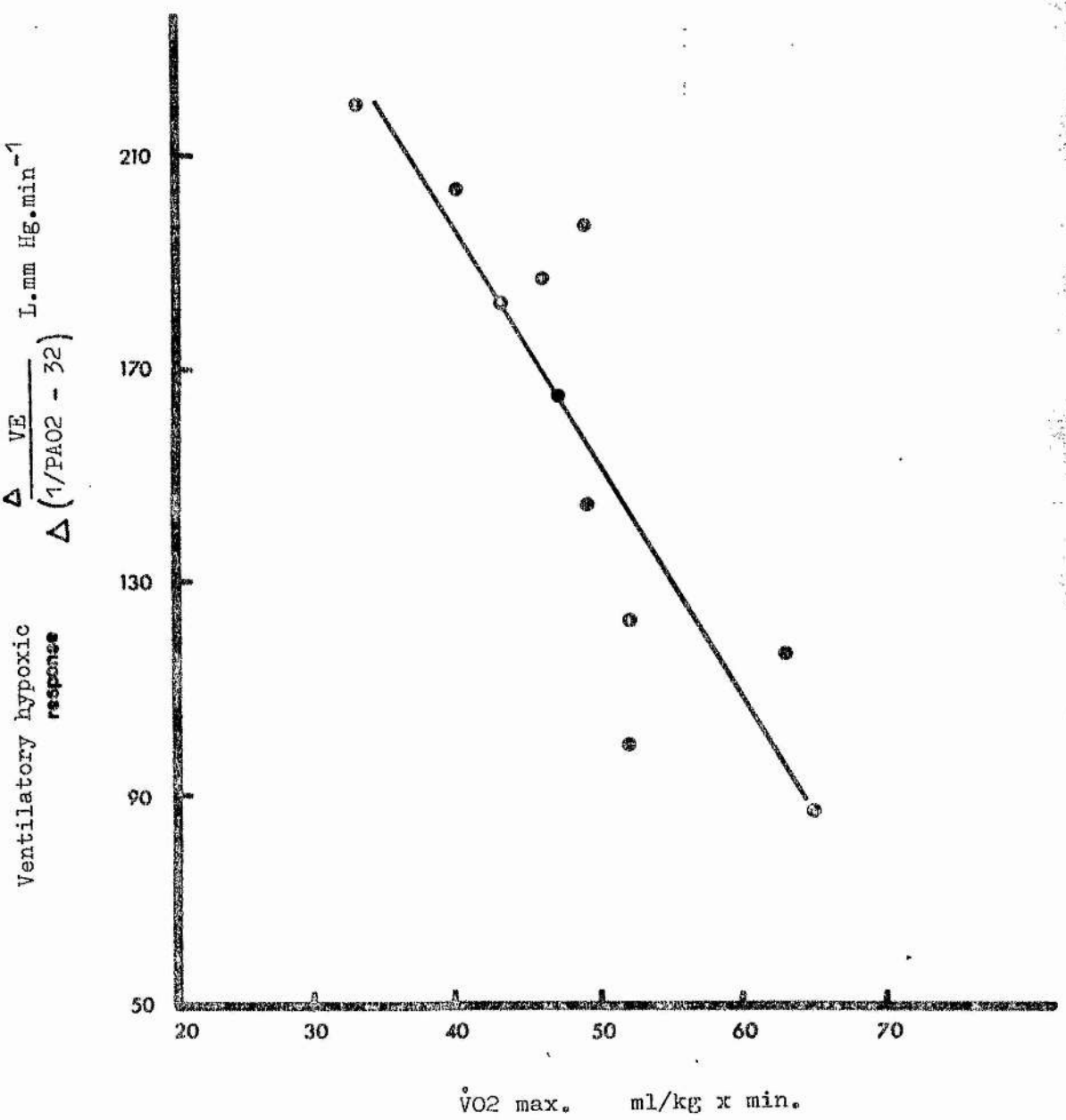


Fig. 2-11a. Correlation between hypoxic ventilatory response and $\dot{V}O_2$ max. for 11 untrained subjects.
r= 0.871 p= < 0.001

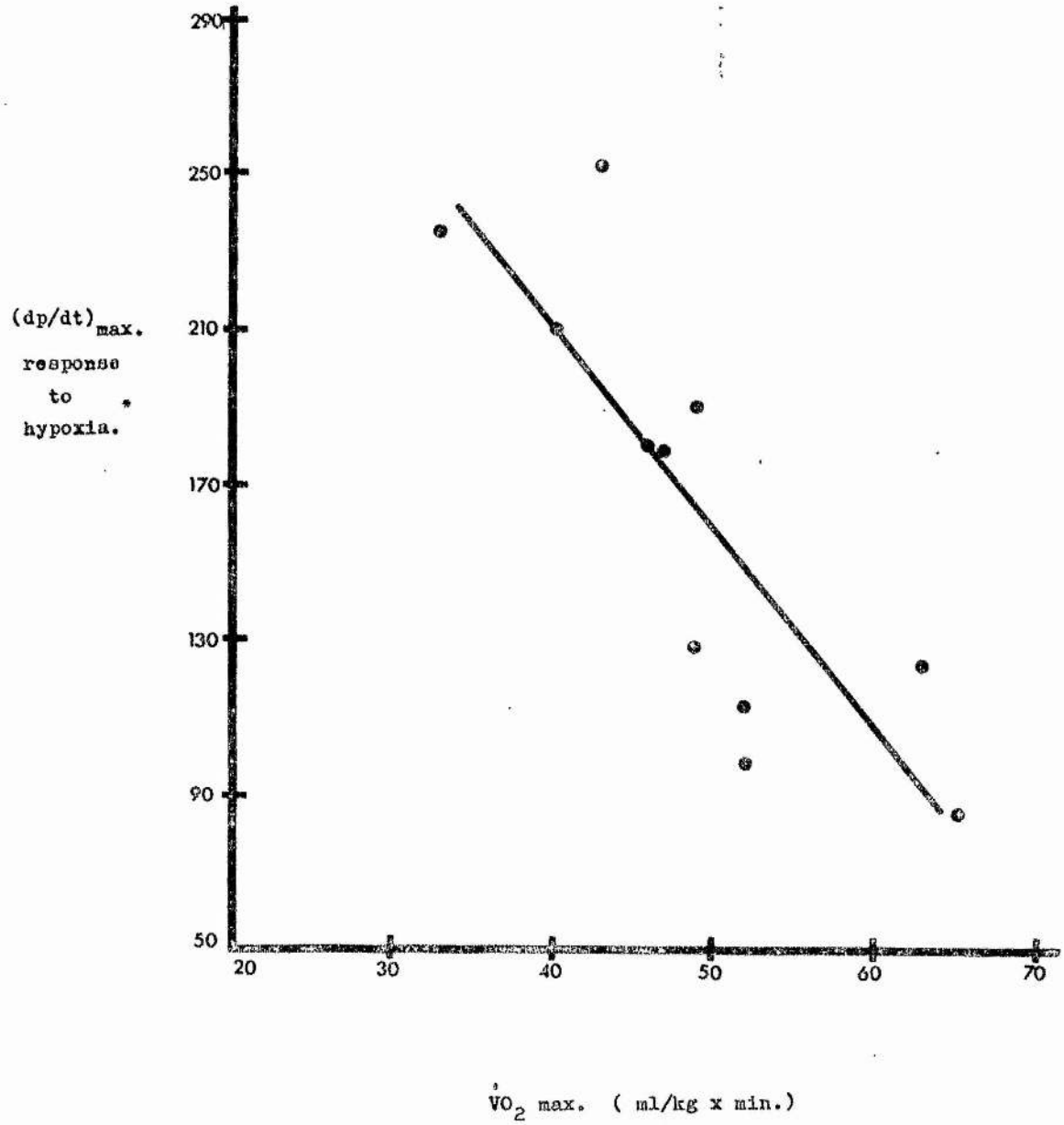


Fig. 2-IIb. Correlation between $(dp/dt)_{max.}$ response to hypoxia and maximum oxygen uptake for the same II untrained subjects as in Fig. 2-IIa. $r = 0.827$ $p = < 0.001$

* y-axis units: $\dfrac{\Delta\,(dp/dt)_{max.}}{\Delta\left(I/_{PAO_2}-32\right)}$ ($cm.H_2O$ mmHg sec^{-I})

Correlation between hypoxic response (at rest) and ventilatory response to exercise.

The 11 untrained subjects who performed the hypoxic drive test had hypoxic drive measured as parameters 'A' and 'A (dp/dt) $_{max.}$'.

a) Hypoxic response and $\triangle \dot{V}_E / \triangle \dot{V}O_2$.

There were significant correlations between hypoxic drive (expressed both as parameters 'A' and 'A (dp/dt) $_{max.}$' and ventilatory response to exercise, when exercise is expressed by oxygen uptake. The correlations are r= 0.811 p= $<$0.01 for the former and r= 0.732 p= $<$0.02 for the later (Fig. 2-12a and Fig. 2-12b).

b) Hypoxic response and $\triangle \dot{V}_E / \triangle \dot{V}CO_2$.

Similar significant correlations were found between hypoxic drive (both parameters ' A ' and ' A (dp/dt) $_{max.}$ ') and ventilatory response to exercise when exercise is expressed as CO_2 production. Correlations between 'A' and exercise response :- r= 0.783 p= $<$ 0.01; and between 'A (dp/dt) $_{max.}$' and exercise response :- r= 0.762 p= $<$0.01 (Fig.2-13a and Fig. 2-13b).

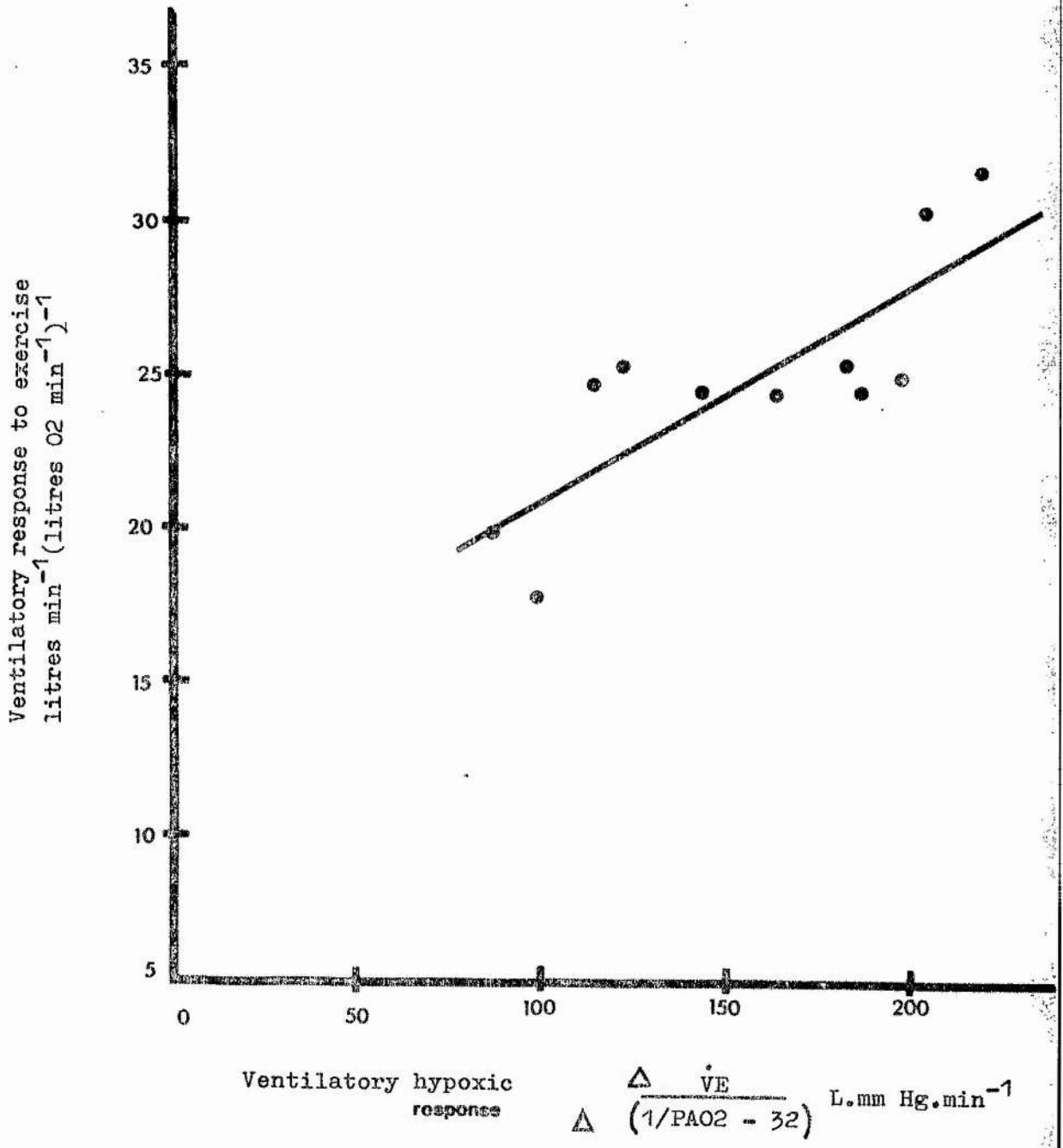


Fig.2-12a. Correlation between ventilatory response to exercise (when exercise is expressed as 02 uptake) and hypoxic ventilatory response at rest in 11 untrained subjects.

r= 0.811 p= < 0.01

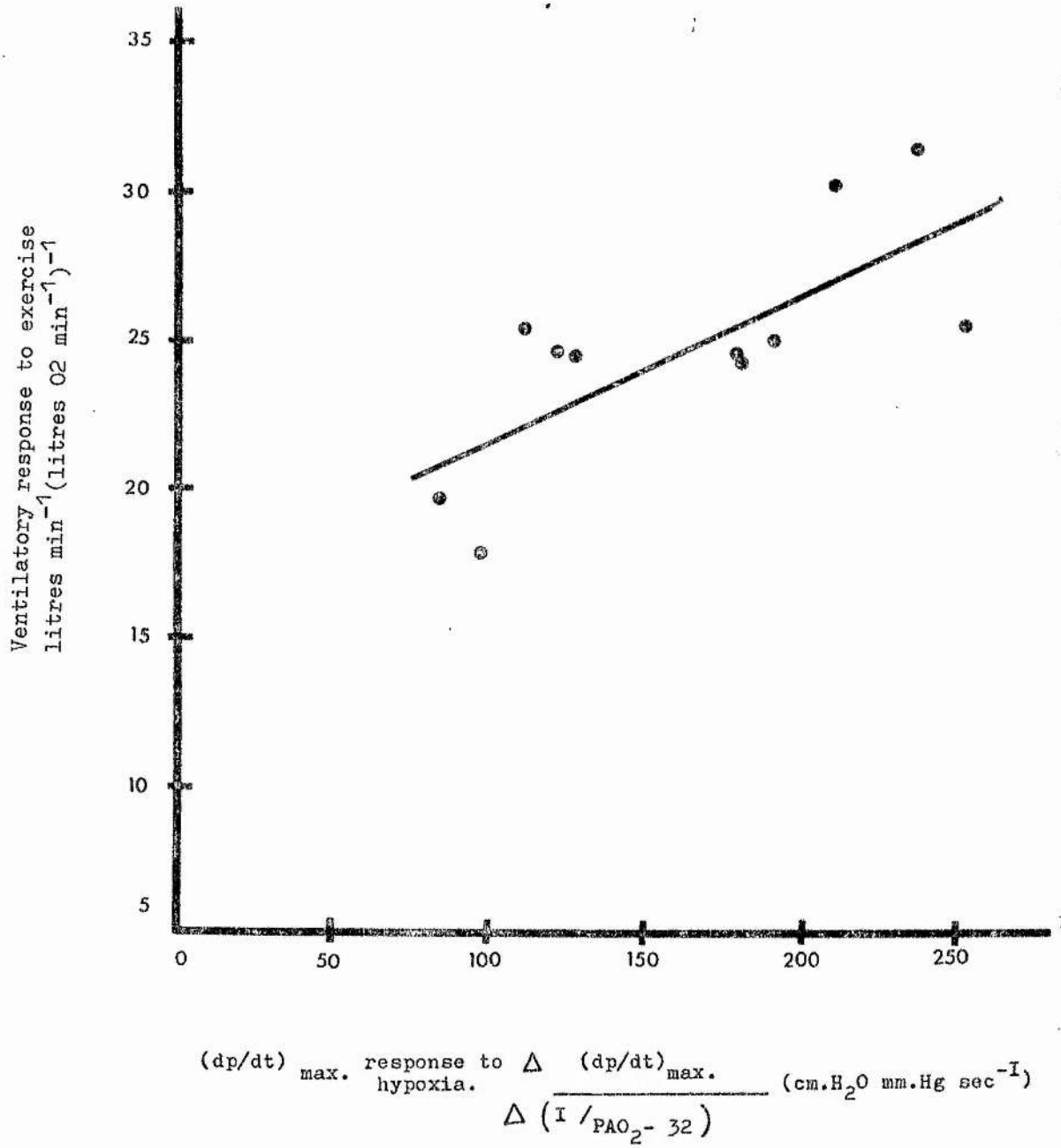


Fig. 2-IIb. Correlation between $(dp/dt)_{max.}$ response to hypoxia and ventilatory response to exercise (when exercise is expressed as O_2 uptake) in the same II untrained subjects as in Fig.2-I2a.
$r = 0.733$ $p =< 0.02$

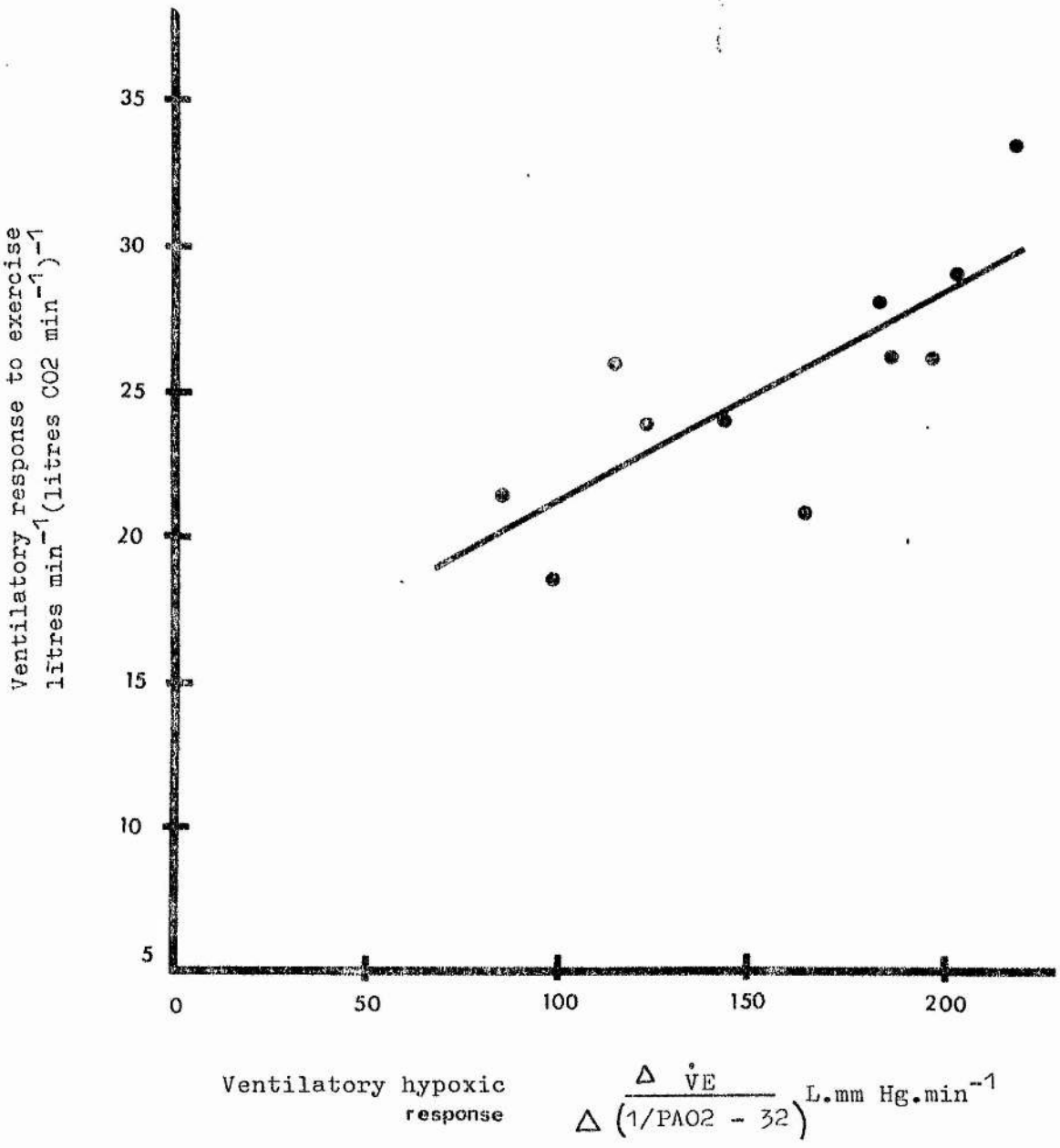


Fig.2-13a. Correlation between ventilatory response to exercise (when exercise is expressed as CO2 production) and hypoxic ventilatory response at rest in 11 untrained subjects.
r= 0.784 p= < 0.01

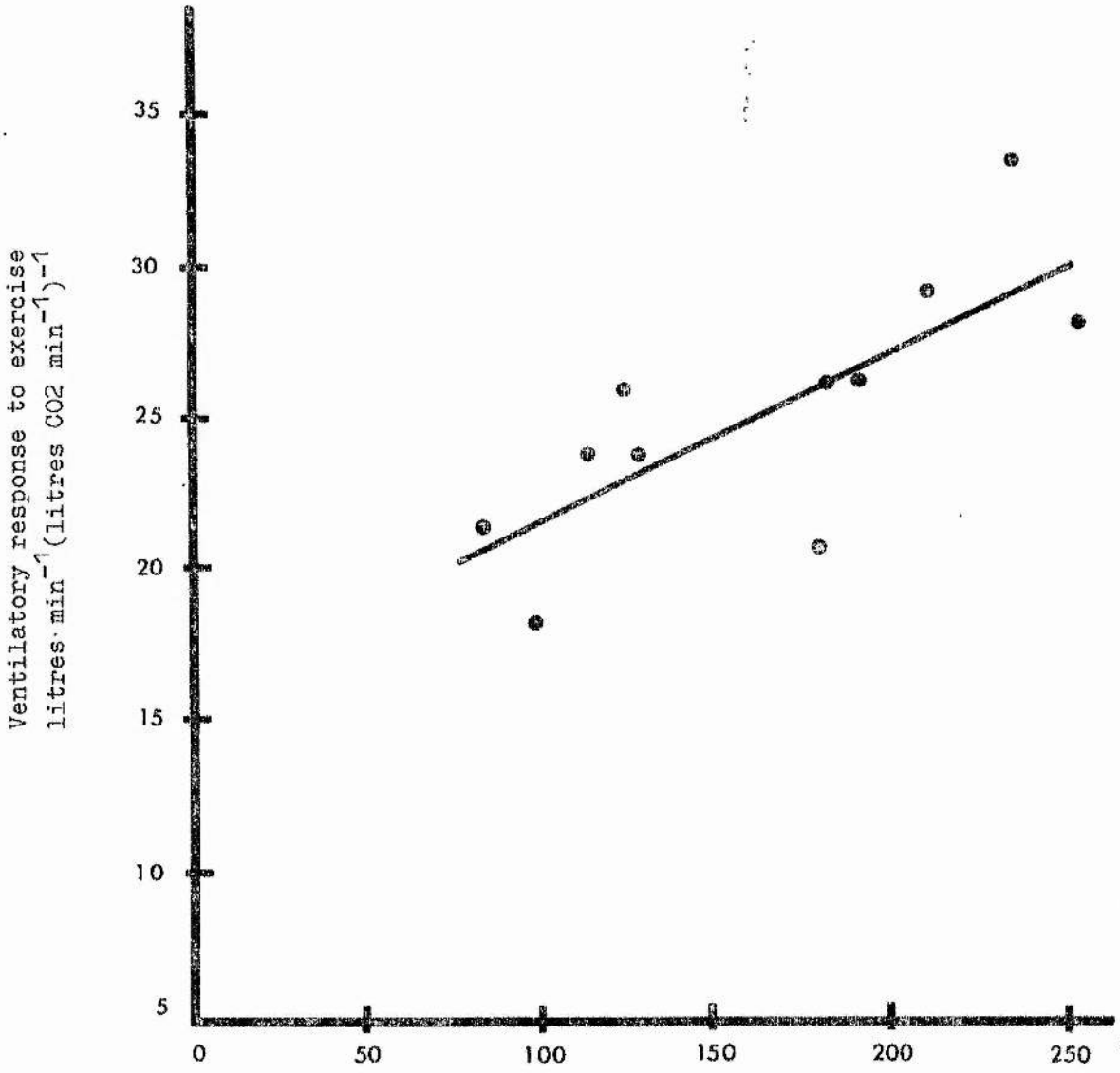


Fig. 2-I3b. Correlation between ventilatory response to exercise (when exercise is expressed as CO_2 produced) and $(dp/dt)_{max.}$ response to hypoxia in the same II subjects (untrained) as in Fig.2-I3a.
r = 0.762 p = <0.0I

Table 2-2. Table showing data on the II untrained subjects undergoing hypercapnic, hypoxic and exercise tests. (see Table I for exercise data).

Subjects.		Ventilatory response to CO_2 S	Ventilatory response to hypoxia. A
4.	GM	3.67	2I9.5
I2.	TM	2.I2	I22.8
I3.	JF	2.97	I96.9
I6.	JK	2.43	I86.7
I7.	PP	3.70	203.7
I9.	KG	2.6I	I64.I
25.	RM	I.40	86.6
28.	MS	2.I5	I43.9
29.	DMI	I.53	II5.0
32.	KL	I.07	98.6
34.	BB	3.I5	I82.3
Mean:		2.44	I56.4
SD:		0.88	45.5
SE:		0.27	I3.7

LOAD	TIME	$\dot{V}CO_2$	$\dot{V}O_2$	$\dot{V}E$
0 kpm/min.	5 mins.	0.38	0.45	15.89
100	5	0.68	0.84	26.59
200	2	0.92	0.87	29.82
300	1	1.18	1.17	37.42
400	1	1.48	1.26	44.76
500	1	1.57	1.43	51.27
600	1	1.80	1.64	58.95
700	1	2.08	1.78	67.96

Sub. No. 8 SC Untrained.
(fig. 2-16b and fig.2-17b)

LOAD	TIME	$\dot{V}CO_2$	$\dot{V}O_2$	$\dot{V}E$
0 kpm/min	5 mins.	0.29	0.33	13.06
100	5	0.47	0.52	18.05
200	2	0.67	0.84	22.92
300	1	0.81	0.92	24.53
400	1	1.07	1.24	30.77
500	1	1.37	1.45	38.56
600	1	1.92	1.76	49.50
700	1	1.96	2.06	59.33
800	1	2.17	2.19	69.94

Sub. No. 2 ZS untrained
(fig 2-16a and fig. 2-17a)

Table 2-3a, showing data obtained during exercise tests for 2 representative untrained subjects.

Units used in Tables 2-3a and 2-3b.

$\dot{V}CO_2$, $\dot{V}O_2$, $\dot{V}E$ - in litres per minute.

LOAD	TIME	$\dot{V}CO_2$	$\dot{V}O_2$	$\dot{V}E$
0 kpm/min.	5 mins.	0.49	0.84	13.96
100	5	0.60	1.01	15.50
200	2	0.58	0.97	14.26
300	1	0.92	1.51	21.37
400	1	0.94	1.47	21.45
500	1	0.96	1.42	21.84
600	1	1.19	1.40	26.56
700	1	1.54	2.82	34.11
800	1	1.72	2.56	38.43
900	1	1.88	2.64	40.64
1000	1	1.76	2.76	43.38
1100	1	2.14	2.97	46.80
1200	1	2.37	3.20	50.63
1300	1	2.87	3.72	59.32
1400	1	3.32	4.05	65.36

Sub. No. 47 GRM trained
(fig 2-16c and fig. 2-17c)

LOAD	TIME	$\dot{V}CO_2$	$\dot{V}O_2$	$\dot{V}E$
0 kpm/min.	5 mins.	0.45	0.73	13.32
100	5	0.47	0.72	14.34
200	2	0.97	0.97	19.20
300	1	0.73	0.97	18.68
400	1	1.20	1.20	21.27
500	1	1.56	1.56	25.47
600	1	1.26	1.66	27.16
700	1	1.90	1.90	30.81
800	1	2.42	2.42	39.36
900	1	2.00	2.76	44.14
1000	1	2.87	2.87	46.87
1100	1	3.04	3.04	54.87
1200	1	3.22	3.22	60.40

Sub. No. 43 SJ trained
(fig. 2-16d and fig. 2-17d)

Table 2-3b, showing data obtained during exercise tests for 2 representative trained subjects.

Table 2-4a. Results of ventilatory and $(dp/dt)_{max.}$ response to CO_2

Subjects.	$\Delta VE/\Delta PCO_2$ $L.min^{-1}\ mmHg^{-1}$	$\Delta(dp/dt)_{max.}/\Delta PCO_2$ $cm.H_2O\ sec^{-1}\ mmHg^{-1}$
3. RD	3.84	3.II
4. GM	3.67	3.73
6. GB	4.04	3.5I
9. PC	2.I5	I.70
I0. DS	2.66	3.40
II. JM	3.80	3.I3
I2. TM	2.I2	I.46
I4. KM	2.53	2.I5
I6. JK	2.43	2.I0
I7. PP	3.70	3.63
I9. KG	2.6I	2.I7
22. PK	2.79	2.6I
25. RN	I.40	I.02
28. MS	2.I5	2.94
33. DW	2.22	2.03
36. KH	3.I3	2.80
Mean	2.83	2.59
SD.	0.78	0.82
SE.	0.20	0.20

Table 2-4b. Results of isocapnic hypoxia test.

Subjects.		Ventilatory response to hypoxia. 'A' $\frac{\Delta V_E}{\Delta (1/PAO_2 - 32)}$ ($L.mm.Hg.min^{-1}$)	$(dp/dt)_{max.}$ response to hypoxia. 'A $(dp/dt)_{max.}$' $\frac{\Delta (dp/dt)_{max.}}{\Delta (1/PAO_2 - 32)}$ ($cm.H_2O$ mm.Hg.sec^{-1})
4.	GM	219.5	235.5
12.	TM	122.8	112.8
13.	JF	196.9	191.0
16.	JK	186.7	181.0
17.	PP	203.7	211.0
19.	KG	164.1	179.8
25.	RN	86.6	84.7
28.	MS	143.9	128.6
29.	DMI	115.0	123.5
32.	KL	98.6	98.5
34.	BB	182.3	253.0
Mean		156.4	163.6
SD.		45.5	57.0
SE.		13.7	17.2

c) Testing validity of using '$A\ (dp/dt)_{max.}$'.

To test whether '$A\ (dp/dt)_{max.}$' can be used as a hypoxia response index, this value is plotted against parameter 'A' (done similarly in Section 1A). There is a significant positive correlation ($r = 0.921$ $p = < 0.001$) between the two parameters (Fig. 2-14)+, confirming the use of $(dp/dt)_{max.}$ as one of measurable responses in respiratory function. (Table 2-4b)

(+ Fig. 2-14 is superimposed in Fig.1A-12in Section 1A).

$\dot{V}O_2$ max.

Using Astrand's $\dot{V}O_2$ max. Prediction Table (Appendix 1), the $\dot{V}O_2$ max. is obtained from heart beat and workload values at submaximal loads. (see table 2-5).

In the 47 subjects studied, $\dot{V}O_2$ max. ranges from 2.0 to 4.4 $L.min^{-1}$ (mean 3.35 SD 0.63 SE 0.09). In the untrained it ranges from 2.0 to 4.4 $L.min^{-1}$ (mean 3.13 SD 0.51 SE 0.08) and is significantly lower ($p = < 0.001$) than values found in the trained which range from 3.8 to 4.4 $L.min^{-1}$ (mean 4.16 SD 0.25 SE 0.08).

When $\dot{V}O_2$ max. is corrected for body weight (see appendix 11), it ranges in the 47 subjects from 31.00 to 74.00 ml/kg x min. (mean 51.04 SD 10.52 SE 1.53). There is a significantly lower $\dot{V}O_2$ max. in the untrained (range 31.00 to 74.00, mean 47.73 SD 9.06 SE 1.49)

Table 2-5.

Table showing data used in VO_2 max. prediction and load at which ventilatory response to exercise slope 'breaks'.

Use for predicting VO_2 max.

Subjects	Heart Rate (beats/min)	Load (kpm/min)	Load Limit* (kpm/min)	Wt. (kg)	V_{O2} max. (litres/min)	V_{O2} max. (ml/kg x min)
1. GJ	170	800	700	68	2.34	34
2. ZS	169	1000	800	61	2.80	46
3. RD	169	1100	700	66	3.20	48
4. GM	168	800	700	70	2.37	33
5. GMD	170	1300	900	66	3.70	55
6. GB	165	600	700	65	2.00	31
7. DB	168	1200	900	72	3.50	49
8. SC	169	900	700	65	2.60	40
9. PC	170	1300	800	63	3.70	59
10. DS	170	1100	800	64	3.14	48

* maximum load before slope 'breaks'.

Table 2-5 (contd)

Subjects.	Heart Rate	Load	Load Limit	Wt.	VO_2 max.	VO_2 max.
11. JM	169	1200	900	70	3.50	50
12. TM	170	1200	800	65	3.40	52
13. JF	170	1200	900	70	3.40	49
14. KM	167	1000	800	70	2.90	41
15. DI	170	1000	700	69	2.86	42
16. JK	170	1000	800	63	2.90	46
17. PP	170	1000	700	73	2.90	40
18. IP	169	800	800	53	2.37	45
19. KG	168	1100	800	68	3.20	47
20. AZ	170	1100	800	61	3.12	45
21. VE	168	1100	900	74	3.20	43
22. PK	168	1100	800	71	3.20	45
23. BP	169	1200	800	55	3.20	58
24. FMG	170	1100	1000	77	3.14	40
25. RN	167	1500	1000	68	4.40	65

Table 2-5 (contd)

Subjects		Heart Rate	Load	Load Limit	Wt.	VO2 max.	VO2 max.
26.	YM	170	900	1000	67	2.60	39
27.	NS	169	1200	900	60	3.50	58
28.	MS	170	1100	700	63	3.14	49
29.	DMI	169	1400	1100	64	4.02	63
30.	HS	168	1100	800	69	3.20	46
31.	FH	169	1300	1000	50	3.70	74
32.	KL	169	1200	1100	67	3.50	52
33.	DW	170	1400	900	69	4.00	58
34.	BB	169	1000	800	68	2.90	43
35.	GML	167	1100	800	68	3.12	46
36.	KH	168	900	800	68	2.60	38
37.	GD	169	900	700	53	2.60	49
Untrained.	Mean				65	3.13	47
	S.D.				5.88	0.51	9.06
	S.E.				0.96	0.08	1.49

Table 2-5 (contd)

Subjects	Heart Rate	Load	Load Limit	Wt.	VO2 max.	VO2 max.
38. SM	167	1500	1100	63	4.40	70
39. JI	169	1300	1200	65	3.80	58
40. AH	167	1400	1100	62	4.10	65
41. NR	169	1300	1100	58	3.80	66
42. DR	168	1500	1100	75	4.40	59
43. SJ	167	1500	1200	67	4.40	66
44. AT	169	1500	1200	62	4.30	69
45. GD	170	1400	1100	73	4.00	55
46. SG	169	1400	1100	67	4.00	60
47. GRM	168	1500	1400	68	4.40	65
Trained	Mean			66	4.16	63
	S.D.			5.18	0.25	4.99
	S.E.			1.64	0.08	1.58
Trained and Untrained	Mean			65	3.35	51
	S.D.			5.69	0.63	10.52
	S.E.			0.83	0.09	1.53

than in the trained (range 55.00 to 70.00, mean 63.30 SD 4.99 SE 1.58) at p= $<$ 0.001 level.

The values above are in general agreement with many findings. Amongst others, Saltin and Astrand 1967 found that, in the untrained males the mean $\dot{V}O_2$ max. of 3.1 $L.min^{-1}$, is significantly lower than those found in rowers (5.1 $L.min^{-1}$) and mid-distance runners (5.4 $L.min^{-1}$). Similar findings were reported by Astrand and Christensen 1964, and Byrne-Quinn et al 1971.

Correlation between $\dot{V}O_2$ max. and response to hypoxia.

In the 11 untrained subjects undergoing the hypoxia test, there were significant negative correlations between $\dot{V}O_2$ max. and hypoxic drive expressed both as parameters 'A' and 'A $(dp/dt)_{max.}$' (r= 0.871 p= $<$ 0.001 and r= 0.827 p= $<$ 0.01 respectively) (Fig. 2-11a and Fig. 2-11b).

Correlation between $\dot{V}O_2$ max. and CO_2 response.

There was a significant negative correlation between $\dot{V}O_2$ max. with CO_2 response in the 47 subjects studied (r= - 0.743 p= $<$0.001) (Fig. 2-10a). In the 16 untrained where CO_2 response was measured both in terms of ventilatory and $(dp/dt)_{max.}$, there was significant negative correlations for both measurements (for $(dp/dt)_{max.}$ response to CO_2 with VO_2 max., r= - 0.746

$p = < 0.001$, and for ventilatory hypercapnic drive with $\dot{V}O_2$ max., $r = -0.741$ $p = < 0.001$) (Fig. 2-10b and Fig. 2-10c).

Correlation between $\dot{V}O_2$ max. and exercise response.

There were significant negative correlations between $\dot{V}O_2$ max. and exercise responses. When exercise was expressed as O_2 uptake, the correlation between $\dot{V}O_2$ max. and this exercise ventilatory response is given by, $r = -0.560$ $p = < 0.001$.

When exercise was expressed as CO_2 output, the correlation between $\dot{V}O_2$ max. and exercise ventilatory response is $r = -0.659$ $p = < 0.001$. (See Fig. 2-10d and Fig. 2-10e).

Correlation between response to hypercapnia and to hypoxia.

In the 11 untrained subjects, there were very significant correlations between ventilatory response to CO_2 and hypoxia. When hypoxia is expressed as parameter 'A', correlation figure is $r = 0.944$ $p = < 0.001$ (Fig. 2-15a) and when hypoxia is expressed as parameter '$A\ (dp/dt)_{max.}$', the correlation figure is $r = 0.913$ $p = < 0.001$ (Fig. 2-15b). These are similar to correlations found in Section 1A. (see Table 2-2).

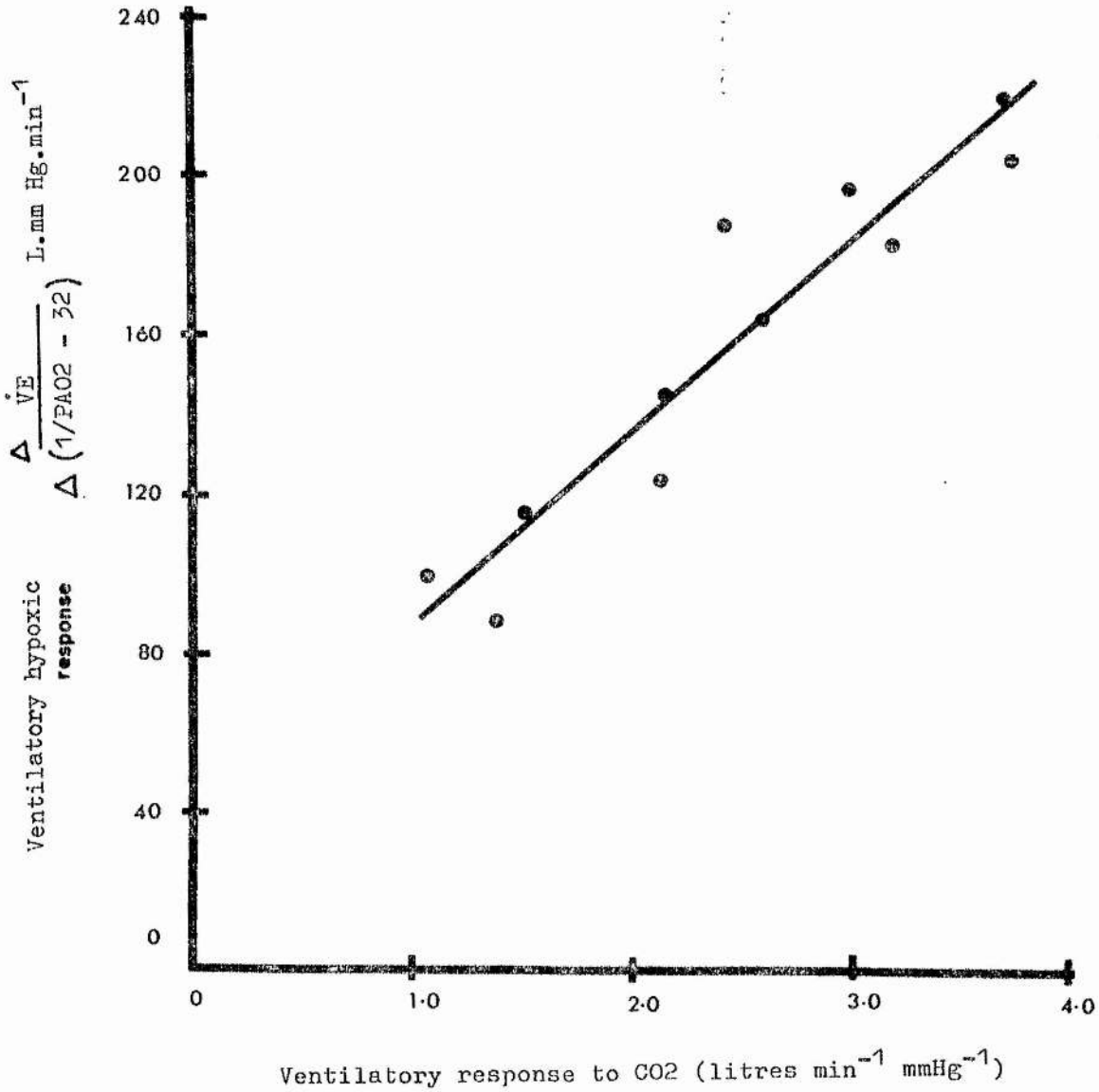


Fig.2-15a. Correlation between hypoxic ventilatory response and ventilatory response to CO2.
r= 0.945 p= < 0.001

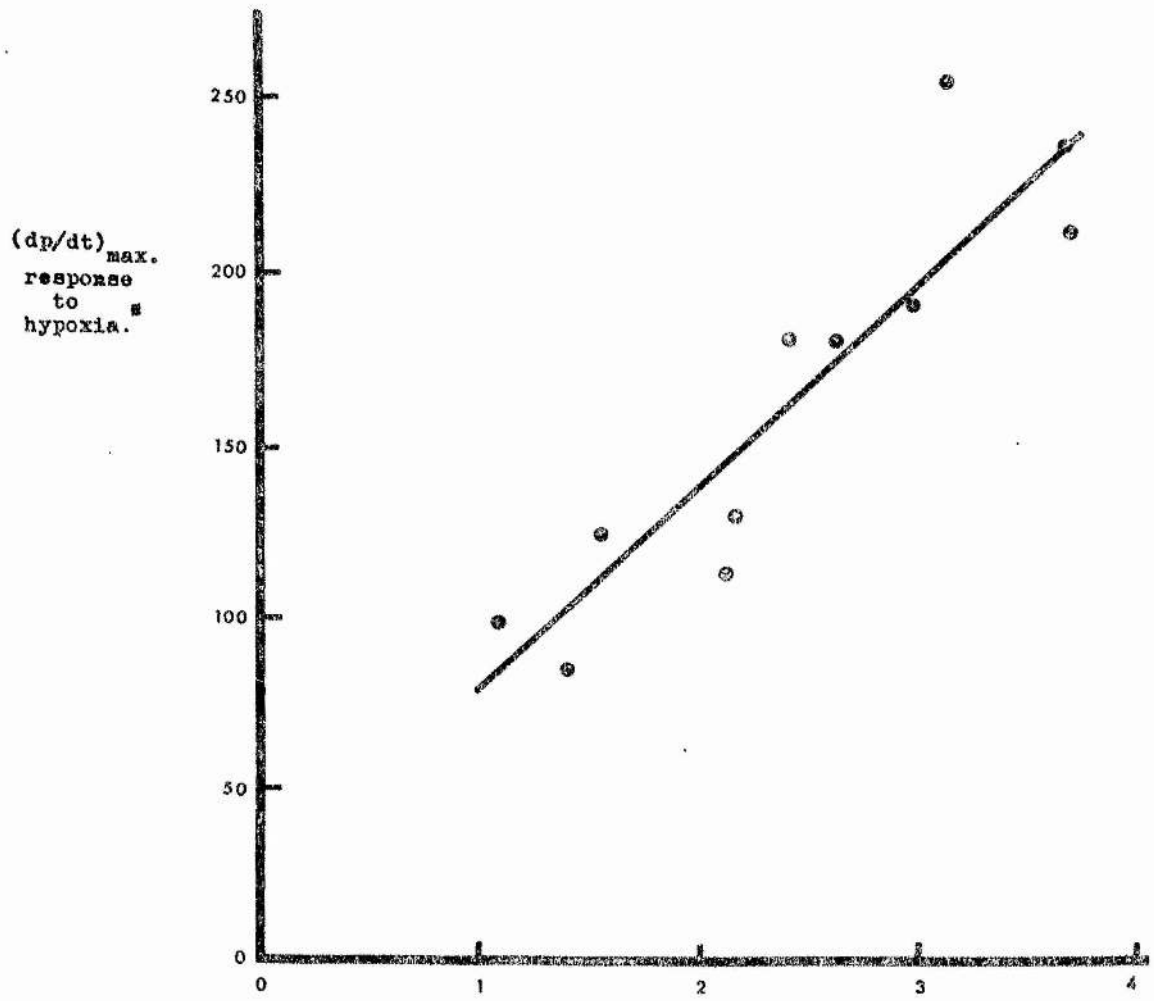


FIG. 2-I5b. Correlation between hypoxic $(dp/dt)_{max.}$ response and ventilatory response to CO_2 in II untrained subjects. $r = 0.913$, $p < 0.001$

* Y axis - units in $\frac{\Delta\ (dp/dt)_{max.}}{\Delta\left(I\ /_{PAO_2} - 32\right)}$ ($cm.H_2O$ $mm.Hg.sec^{-I}$)

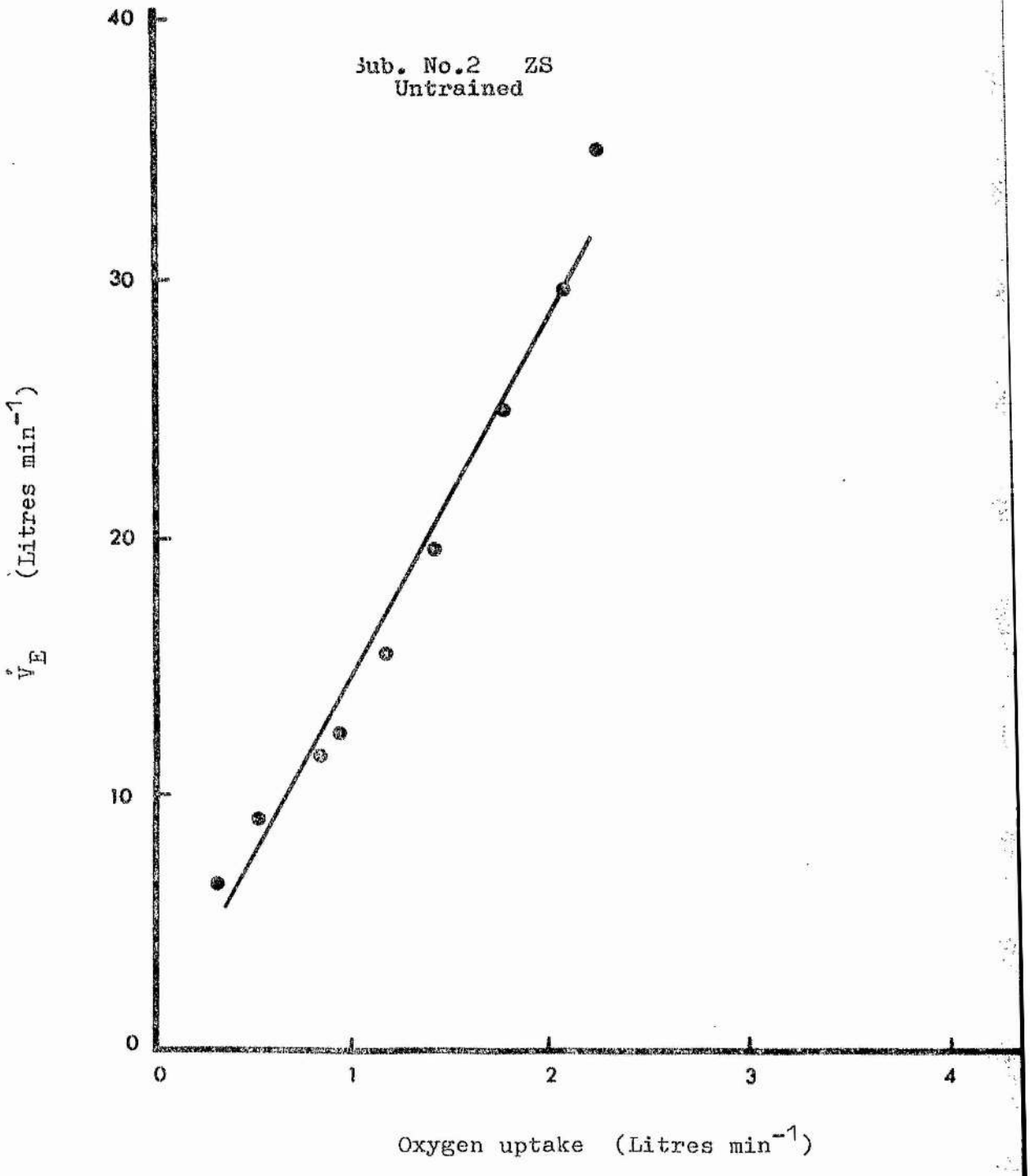


Fig. 2-16a. Linear part of slope of ventilation against oxygen uptake in one subject.
slope = 29.04 litres min^{-1} (litres O2 min^{-1})$^{-1}$

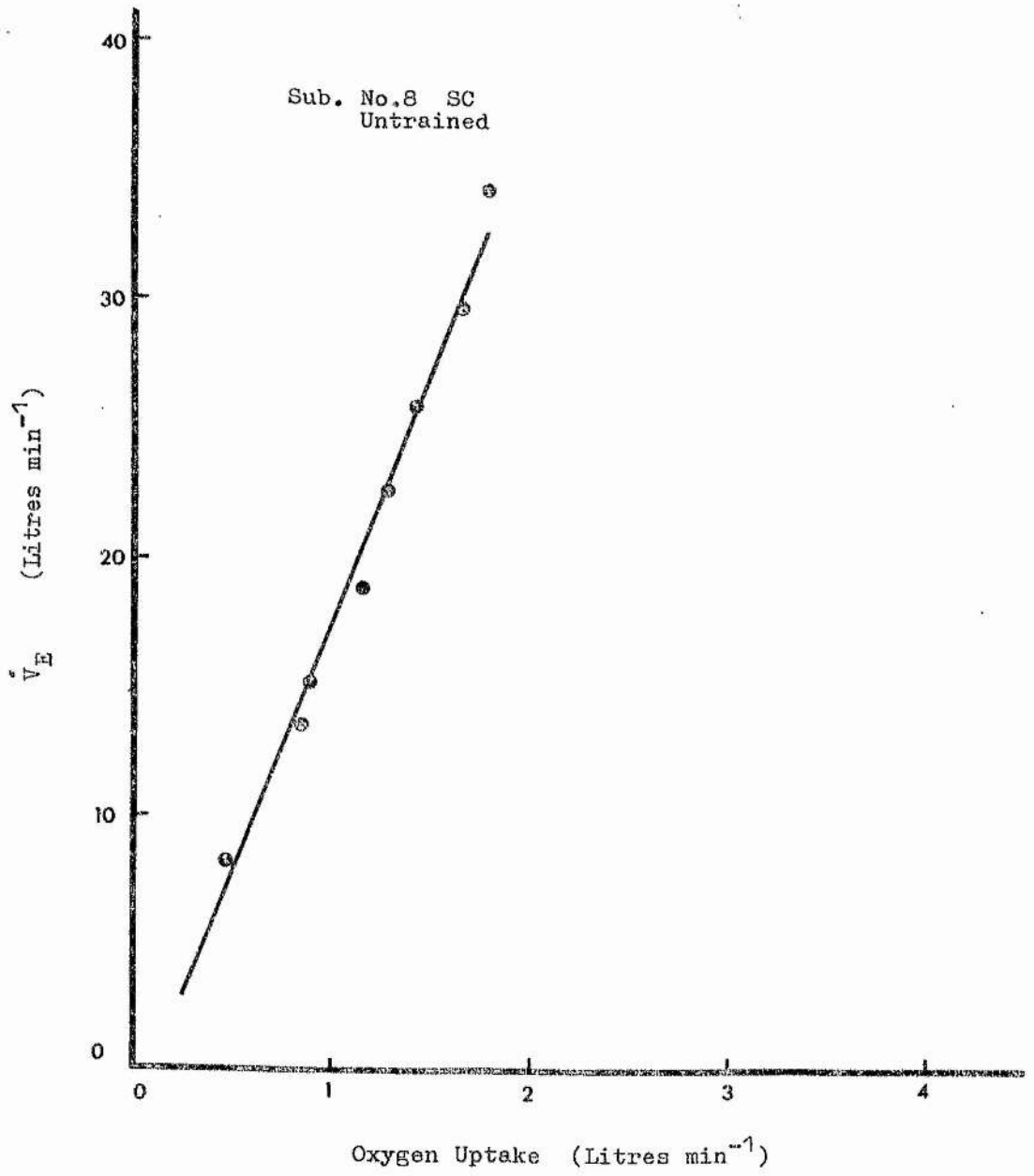


Fig. 2-16b. Linear part of slope of ventilation against oxygen uptake in one subject.
slope = 37.57 litres min^{-1} (litres O2 min^{-1})$^{-1}$

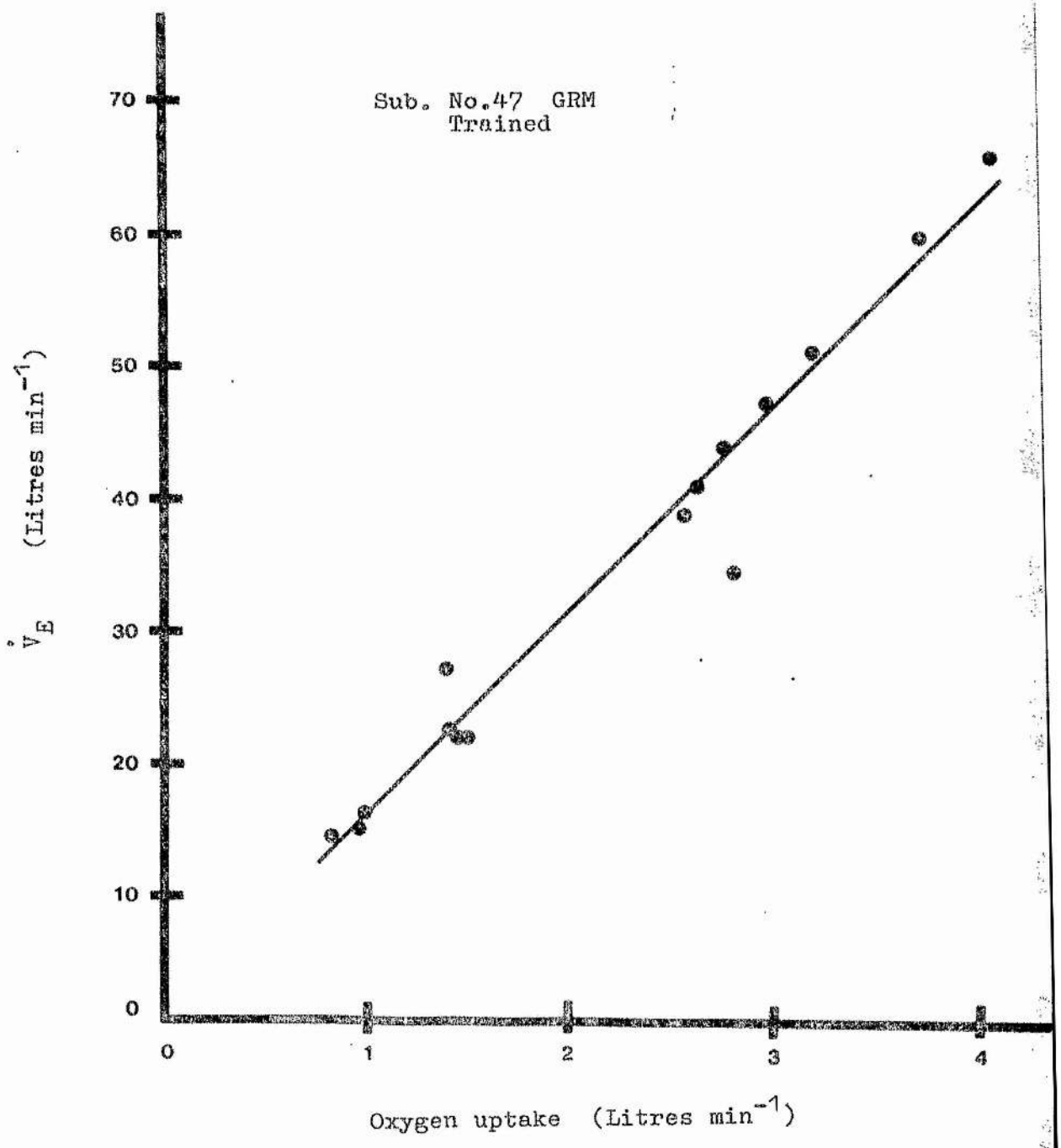


Fig. 2-16c. Linear part of slope of ventilation against oxygen uptake in one subject.
slope = 15.59 litres min^{-1} (litres O2 min^{-1})$^{-1}$

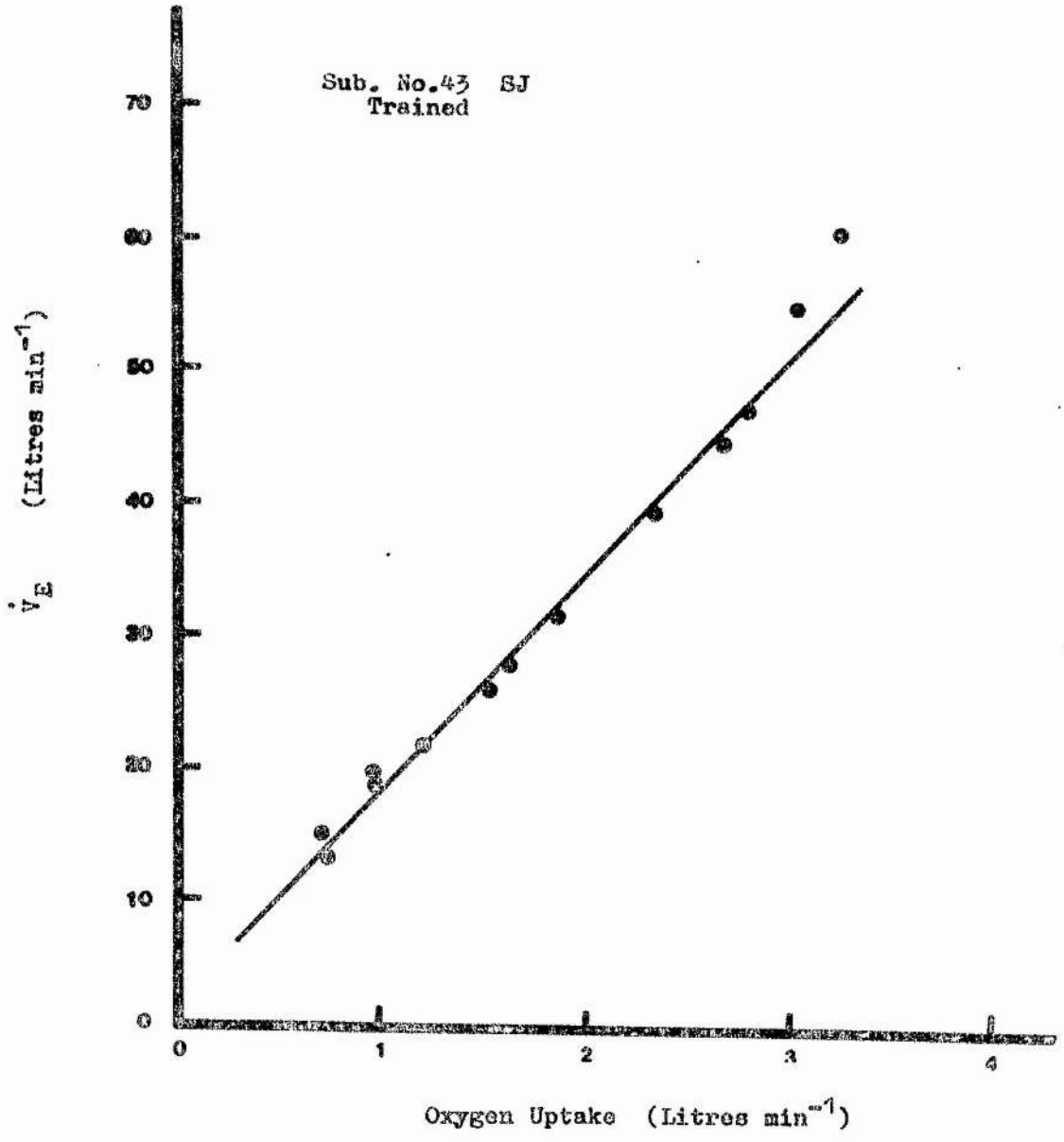


Fig. 2-16d. Linear part of slope of ventilation against oxygen uptake in one subject.
slope = 19.18 litres min^{-1} (litres O2 min^{-1})$^{-1}$

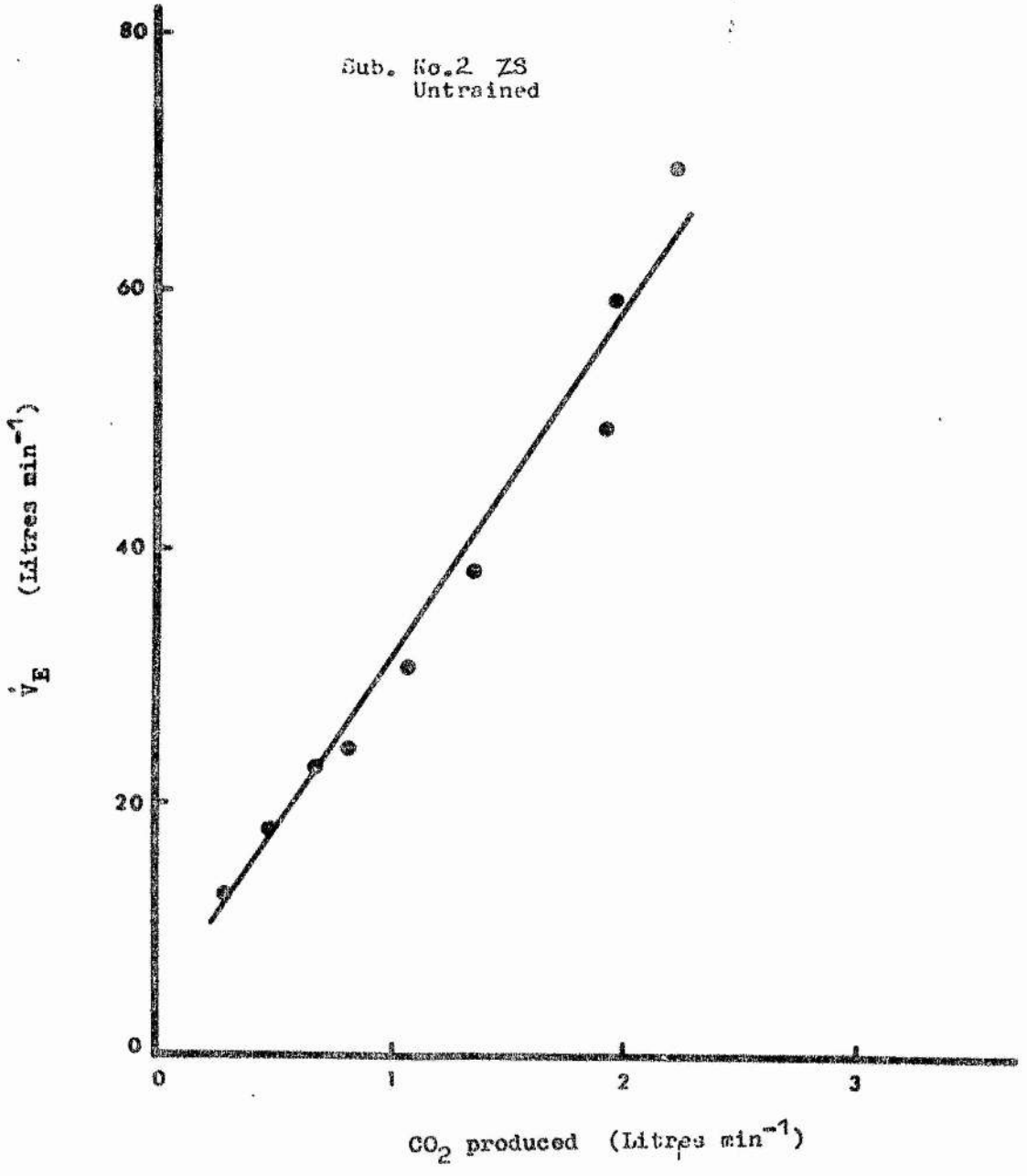


Fig. 2-17a. Linear part of slope of ventilation against CO2 production in one subject.
slope = 27.55 litres min^{-1} (litres CO_2 min^{-1})$^{-1}$

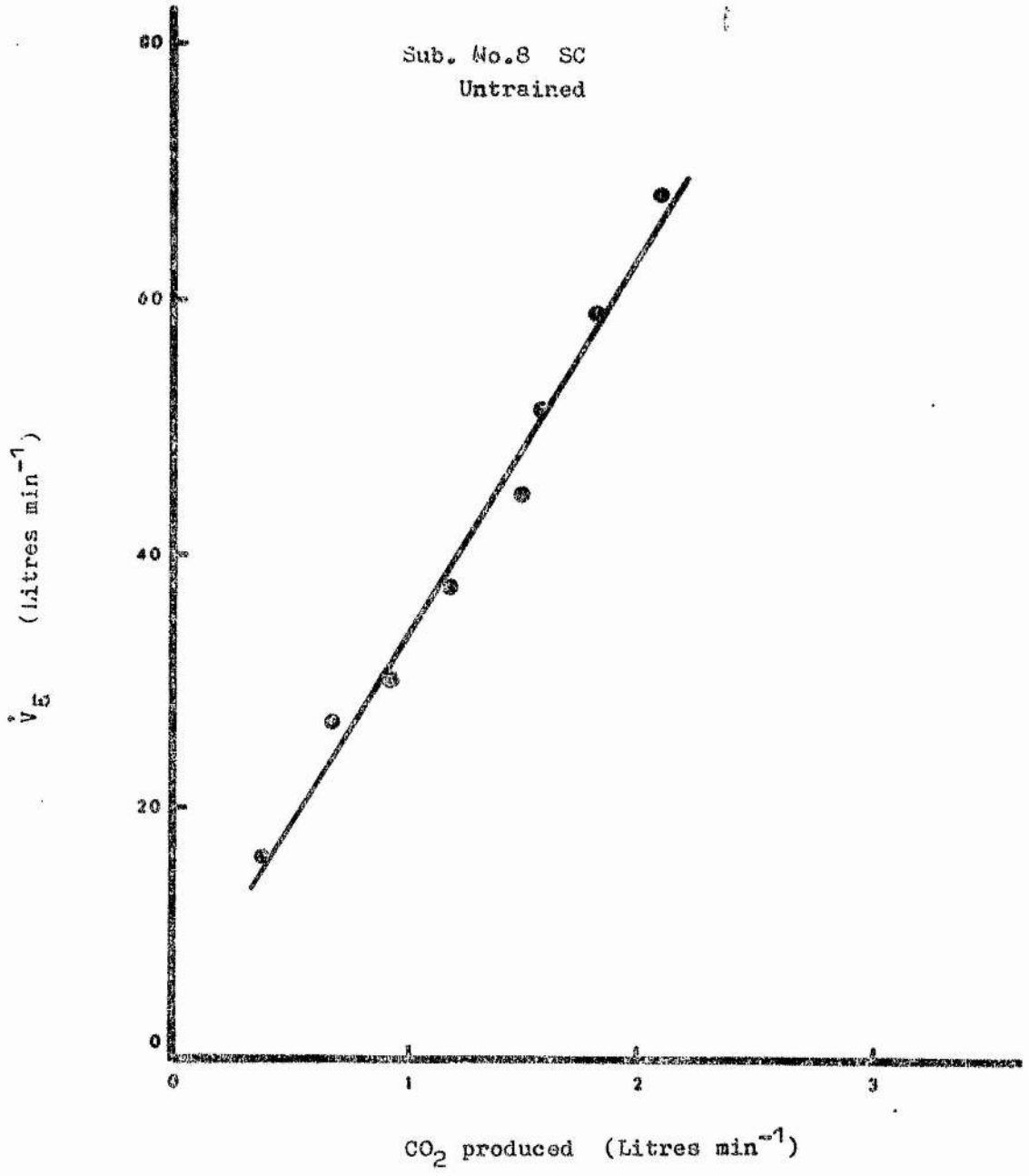


Fig. 2-17b. Linear part of slope of ventilation against CO_2 production in one subject.
slope = 29.46 litres min^{-1} (litres CO_2 min^{-1})$^{-1}$

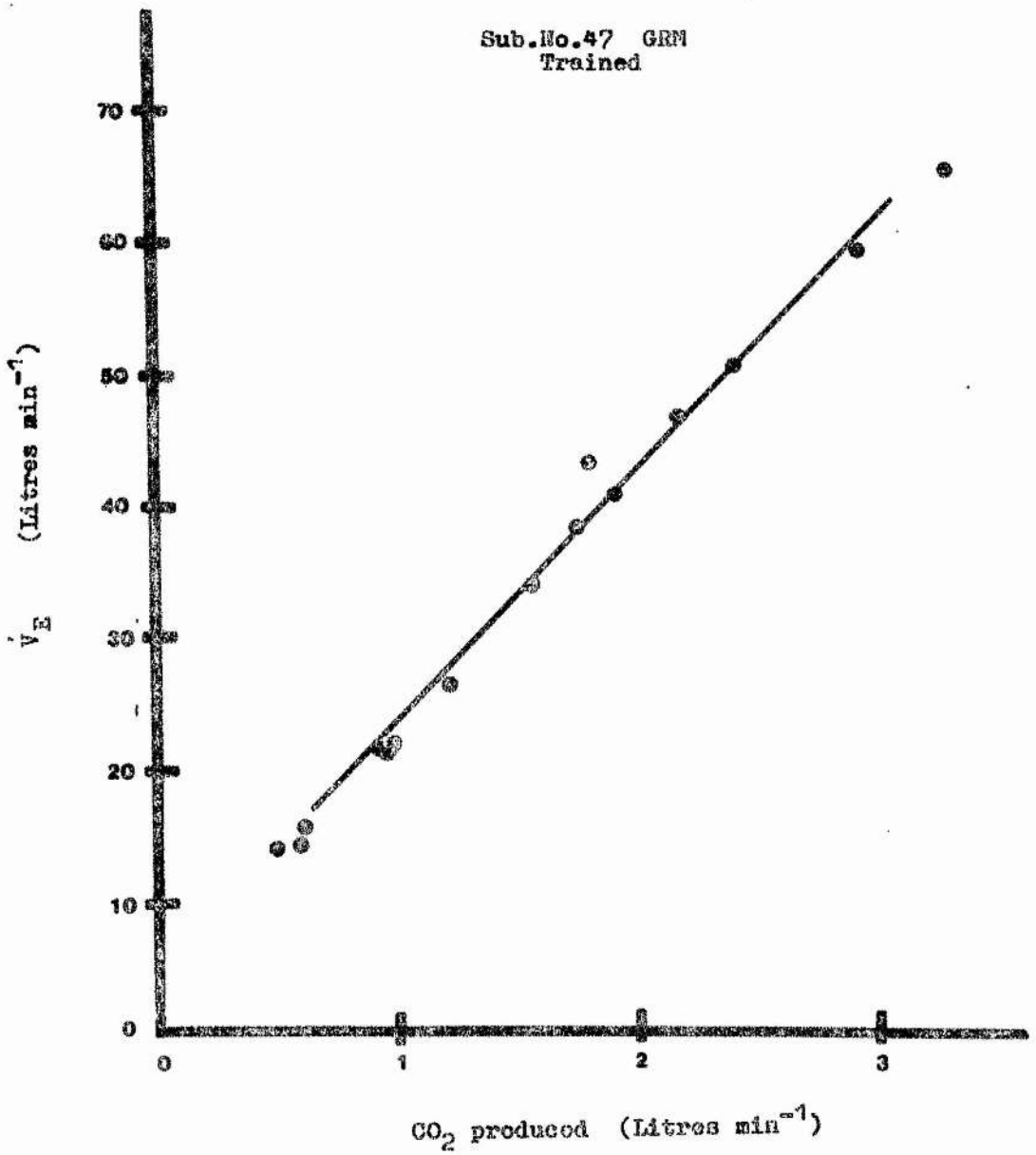


Fig. 2-17c. Linear part of slope of ventilation against CO_2 production in one subject.
slope = 19.29 litres min^{-1} (litres CO_2 min^{-1})$^{-1}$

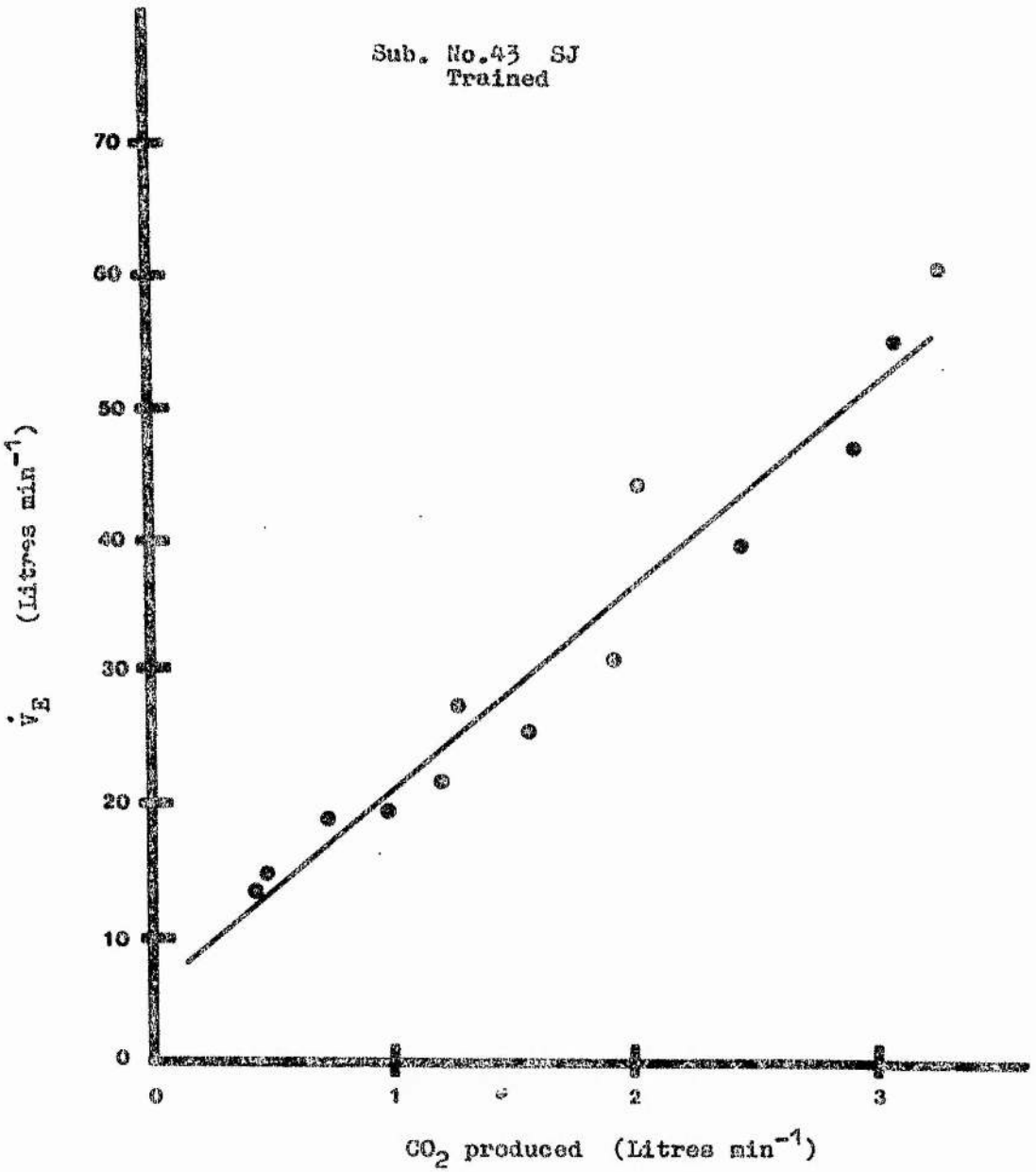


Fig. 2-17d. Linear part of slope of ventilation against CO_2 production in one subject.
slope = 19.05 litres min^{-1} (litres CO_2 min^{-1})$^{-1}$

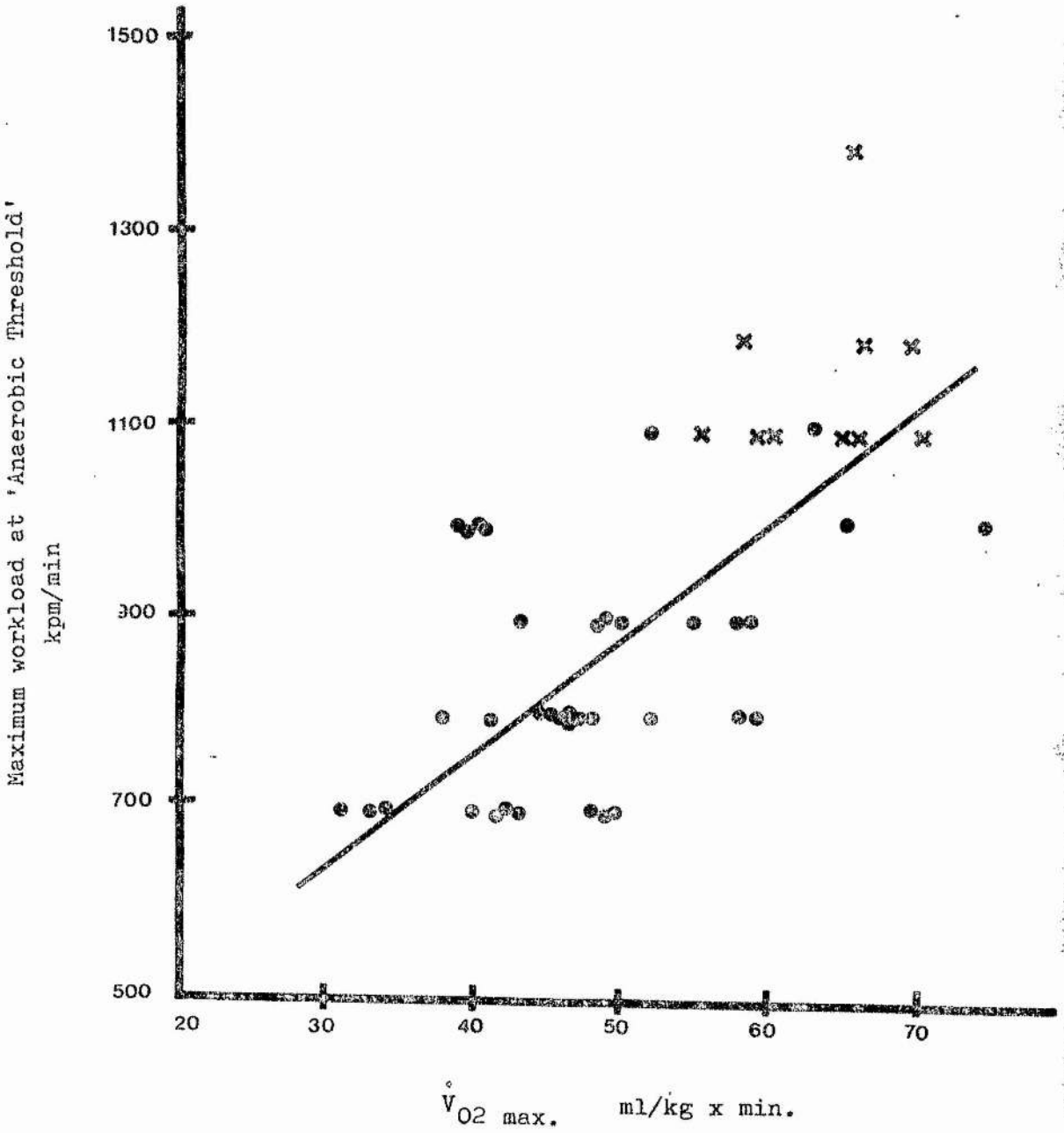


Fig. 2-18. Correlation between maximum workload in kpm/min at which 'Anaerobic Threshold' occurs and 'Physical Fitness' measured as $\dot{V}_{O2\ max.}$ in ● 37 untrained and ✖ 10 trained subjects.

r= 0.731 p= < 0.001

Records of data on exercise studies.

Tables 2-3a and 2-3b show typical records made for 2 untrained and 2 trained subjects. It records $\dot{V}_E$, $\dot{V}CO_2$ and $\dot{V}O_2$ from the linear part of the measured ventilatory exercise slopes $\Delta\dot{V}_E / \Delta \dot{V}O_2$ and $\Delta\dot{V}_E / \Delta \dot{V}CO_2$. (Data shown for subjects No. 43 SJ (trained) is taken from the second set of readings, to show repeat experiment data).

Use of $(dp/dt)_{max.}$ as a response measurement in this study.

The use of $(dp/dt)_{max.}$ as a response measurement at rest shows that it is comparable with ventilatory response. Results which show significant correlations with $(dp/dt)_{max.}$ response ($\dot{V}O_2$ max. and exercise responses) also show similar correlation with ventilatory response. Also as shown in Section 1A, changes in ventilation paralleled changes in $(dp/dt)_{max.}$ during hypercapnia and hypoxia tests. This further confirms the use of $(dp/dt)_{max.}$ as a response measurement given in Section 1A. (see Tables 2-4a and 2-4b).

Initial trials with $(dp/dt)_{max.}$ measurements were made during exercise studies to get slopes of $\Delta (dp/dt)_{max.} / \Delta\dot{V}O_2$ and $\Delta(dp/dt)_{max.} / \Delta\dot{V}CO_2$. The increase in FRC during moderate exercise may introduce errors into the $(dp/dt)_{max.}$ readings. Moreover, the two-way valve used would give a slightly increased resistance, affecting

normal exercise ventilation. However, if measurements of response in very mild exercise is warranted, the use of $(dp/dt)_{max.}$ is possible.

Construction of exercise ventilatory response slopes.

In this study, the linear part of the $\Delta \dot{V}_E / \Delta \dot{V}O_2$ and $\Delta \dot{V}_E / \Delta \dot{V}CO_2$ slopes was used for the measurement of ventilatory response to exercise. To find the linear part, the graph is plotted for $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}_E$ for the whole duration of exercise. The point at which there is a break in the linearity is then selected and the points after it discarded. The straight line slope is then constructed from the remaining points using a computer graph plotter by method of least squares regression. In nearly all the subjects, the AT break occurs at nearly the same point on both the $\Delta \dot{V}_E / \Delta \dot{V}O_2$ and $\Delta \dot{V}_E / \Delta \dot{V}CO_2$ slopes.

DISCUSSION.

Ventilatory response to exercise: $\triangle \dot{V}_E / \triangle \dot{V}O_2$ slope.

In addition to measuring the ventilatory response to exercise, the slopes also measures the linear part of the slopes of 'ventilatory equivalents' for oxygen in exercise, which is given by $\dot{V}_E / \dot{V}O_2$ (similarly $\dot{V}_E / \dot{V}CO_2$ is ventilatory equivalent for CO_2). At moderate exercise, the pulmonary ventilation is closely adjusted to the metabolic needs of the body, so the ventilatory equivalents ($\dot{V}_E / \dot{V}O_2$ or $\dot{V}_E / \dot{V}CO_2$) remain quite constant. This is more a metabolic function in that, for a given ventilation, a given volume of oxygen is used. Thus in this experiment subjects performed dynamic exercise, employing large muscle groups at a number of increasing metabolic loads. At each power output (or load increase on the cycle ergometer), $\dot{V}O_2$ is the independent variable whereas $\dot{V}_E$ is the measured response. Oxygen uptake is used as an index of power load imposed upon ventilation, as oxygen uptake increases with load. Measurement of ventilation, tidal volume and breathing frequency can also be used as indices of the ventilatory responses. In this study ventilation is used as the ventilatory response index.

As $\dot{V}O_2$ is directly proportional to work load, the measurement of $\dot{V}O_2$ somewhat gives the load or an index of power load, whereby increases in $\dot{V}O_2$ would mean increases in load with $\dot{V}_E$ as the resulting response. In

other words $\dot{V}O_2$ is a metabolic load as opposed to external ergometric load. It is shown that normals (Weil et al 1972) and normals, trained and untrained (Irma-Astrand 1960) doing the same workload shows the same $\dot{V}O_2$ (on cycle ergometers). Hermansen and Oseid 1971, also showed similar results on treadmill exercise. However in obese subjects, this relationship differs from normals in that they show a decrease in $\dot{V}O_2$ with equivalent work loads (Davis et al 1975). Also Cotes et al 1969, showed that on average, $\dot{V}O_2$ were higher in heavy than light subjects, but these differences were significant only at 10% level of probability. Allen et al 1968 showed that the change of oxygen consumption at a fixed work load was very slight in all his modes of exercise (progressive bicycle, step and treadmill).

Cotes et al 1969 and Allen et al 1968 showed that regression of ventilation on $\dot{V}O_2$ during submaximal progressive and steady state exercise are identical. Spiro et al 1974, suggested that the slope of linear relationship between $\dot{V}_E$ and $\dot{V}O_2$ can be used as a measure of the fitness of an individual as it indicates an increase in $\dot{V}_E$ that is obligatory for an increase in energy expenditure equivalent to an additional oxygen uptake of 1 Litre / min.

Pulmonary ventilation increases during muscular exercise in proportion (rectlinearly) to the increase in energy expenditure up to approximately 55% to 75% of an individual's aerobic capacity. Beyond this point the ve-

ntilation increases out of proportion to energy expenditure (curvilinear increase - the hyperventilation of physical exercise) probably due to an acidemic stimulus secondary to production of lactic acid, (Wasserman et al 1967, Hughes et al 1968, Comroe 1965). This inflection point is often reffered to as 'Anaerobic threshold', (AT). This also applies to $\dot{\Delta V}_E / \dot{\Delta V}CO_2$ curve for identical reasons, but the spread between subjects and the deviation of linearity is less marked than for $\dot{\Delta V}_E / \dot{\Delta V}O_2$, (Wasserman et al 1967). This metabolic acidosis results in respiratory compensation, increasing alveolar ventilation to eliminate the extra CO_2 produced. Since this is the case, the rectilinear part of the slopes (which is somewhat equivalent to submaximal part of exercise) is taken to measure the $\dot{\Delta V}_E / \dot{\Delta V}O_2$ and $\dot{\Delta V}_E / \dot{\Delta V}CO_2$. (Rebuck et al 1972).

Similarly Wasserman et al 1973 and Kalson et al 1971 found that during progressive cycle ergometer exercise, there is no increase in blood lactate level until work load reaches 50% to 60% of the maximum work load. After this threshold is reached, there is a progressive increase in blood lactate with increasing workload.

Ventilatory response to exercise: $\Delta \dot{V}_E / \Delta \dot{V}CO_2$ slope.

Wasserman et al 1967 have shown that with exercise at sea-level, ventilation is correlated better (being less variable and more linear) with $\dot{V}CO_2$ rather than $\dot{V}O_2$, suggesting that ventilation is geared more closely to CO_2 than to O_2 metabolism. Also Fagraeus et al 1974, showed that the standard deviation for $\dot{V}_I$ / $\dot{V}O_2$ was generally bigger at any given work load than for $\dot{V}_I$ / $\dot{V}CO_2$. Similarly they found that the relationship between $\dot{V}_I$ / $\dot{V}CO_2$ was more linear than between $\dot{V}_I$ / $\dot{V}O_2$. These observations suggest that $\dot{V}_I$, in the steady state of exercise, has a closer functional coupling with $\dot{V}CO_2$ than with $\dot{V}O_2$.

Hughes et al 1968, showed that when ventilation is expressed in terms of CO_2 output, there is a narrow range among normal subjects, variations mainly due to differences in aveolar ventilatory response to exercise. Subjects with lower arterial PCO_2 have a high ventilatory response and vice versa. Jones et al 1966, constructed a series of $\Delta \dot{V}_E / \Delta \dot{V}CO_2$ isopleths of different slopes for different $PaCO_2$.

There are two main factors which determine the $\Delta \dot{V}_E / \Delta \dot{V}CO_2$ relationship, i.e. tidal volume-dead space ratio (VD/VT) and alveolar ventilation. In normal subjects the VD/VT changes quite predictably (Jones et al 1966) and many workers have shown that $PaCO_2$ remains virtually constant throughout the linear part of the ventilatory response to exercise, showing that VA is increasing in dir-

ect proportion to $\dot{V}CO_2$. Thus the isopleths of Jones et al 1966 showed that in normals, those having higher $PaCO_2$ have lower $\Delta \dot{V}_E / \Delta \dot{V}CO_2$ slopes and vice versa.

It is also reported that the linear increase of $\dot{V}_E$, $\dot{V}CO_2$ and $\dot{V}O_2$ with work rate, below the 'anaerobic threshold' is similar under 4 to 6 minutes, incremental work (measurements made during last minute of each work rate) and 1 minute incremental work (continous measurements) (Wasserman et al 1973). Whipp and Wasserman 1972, in experiments to find the effects of work intensity on time course of oxygen uptake during constant-load exercise, found that (with computer display on-line $\dot{V}O_2$ for each breath) $\dot{V}O_2$ steady-state time is reached within 3 minutes at low work rate (under conditions of steady-state, $\dot{V}O_2$ and $\dot{V}CO_2$ is linearly related to work rate). Thus it can be seen from this that the realtionships between $\dot{V}_E$ and $\dot{V}O_2$ or $\dot{V}CO_2$ in progressive exercise tests are identical to those obtained in steady-state exercise.

In this study both the exercise response slopes ($\Delta \dot{V}_E / \Delta \dot{V}CO_2$ and $\Delta \dot{V}_E / \Delta \dot{V}O_2$) were linear up to about the same workload. This showed that both the slopes are reliable as a measurement of exercise ventilatory response in this study.

PCO_2, PO_2 and pH changes in arterial blood during exercise.

a) PaO_2 in exercise.

There is a wide variation of findings reported in the analysis of PaO_2 during exercise. This may be to a great extent due to the fact that the examinations were made at different work loads in relation to the working capacity. Thus a moderate load for one subject is a mild load for another. However in most cases, at submaximal loads, changes are small except when the load gets heavier. Thus Asmussen and Neilsen 1958 and Lambertsen et al 1959, found that the O_2 tension of arterial blood increases during exercise. On the other hand Lilienthal et al 1946, Filley et al 1954, Holmgren and Linderholm 1958 and Linderholm 1959 found PaO_2 to decrease with exercise. Suskind et al 1950, during continous exercise measurements found an initial decrease in PaO_2 and then an increased PaO_2. Similar results were obtained by Barr et al 1964, who found an initial decrease, followed by an increase and a plateau. However Mitchell et al 1958, Asmussen and Neilsen 1960, Matell 1963, Dejours 1964, Wasserman et al 1967 and Whipp and Wasserman 1969 did not notice any significant changes in PaO_2 from control to high loads of exercise. There is a wide acceptance of the fact that during moderate exercise, PaO_2 does not change appreciably so as to contribute a significant factor in exercise hyperpnea. This however does not mean that the hypoxic chemoreflex drive during exercise is unchanged or decre-

ased. Increasing the PaO_2 by O_2 administration significantly decrease ventilation (Asmussen and Neilsen 1946), the decrease being more so as the work gets heavier (Lambertsen et al 1959, Bannister and Cunningham 1954).

Since PaO_2 does not fall with exercise and as it is shown that there is an oxygen chemoreflex drive during exercise, this drive must interact with other factors to give this hyperpnea (Asmussen and Neilsen 1958). It has been shown that O_2 and CO_2 drive are facilitory (Asmussen and Neilsen 1957, and Lloyd 1963).

b) $PaCO_2$ in exercise.

As with measurements of PaO_2, there is a wide variation of $PaCO_2$ reported. Direct as well as indirect measurements shows a decrease, increase and also fluctuations of $PaCO_2$ with exercise. As with measurements of PaO_2, this wide variations may be due to the fact that measurements were made at different work loads in relation to the working capacity. By direct measurements, in submaximal exercise, Enghoff 1938, Hickham et al 1951 and Holmgren and Linderholm 1958 reported an increase in arterial PCO_2 whereas fluctuations within normal range of variation in $PaCO_2$ were reported by Liliethal et al 1946, Suskind et al 1950, Filley et al 1954, Asmussen and Neilsen 1956 and Linderholm 1959. Dejours 1964 and Matell 1963 reported a slight increase in $PaCO_2$ using a direct measurement. Indirect $PaCO_2$ measurement by Taylor 1941 and

Comroe 1944 showed a decrease whereas Bannister et al 1954 showed an increased value.

There is however general agreement that during exercise there is a slight increase in $PaCO_2$ from control levels to moderate exercise.

c) Arterial pH in exercise.

Here there is a wide agreement with the fact that pH does fall during exercise. In moderate exercise, Matell 1963, Hughes et al 1968, Dejours 1964, Barr et al 1964, reported falls in pH. The pH decrease is slight in mild exercise, the fall being more prominent with exercise intensity (Dejours 1964), with slight shift to acidosis occuring during moderate exercise (Galdston and Wollack 1947, Hickham et al 1951, Filley et al 1954, and Asmussen and Neilsen 1958) and increasing fall in pH with higher loads (Mitchell et al 1958, Holmgren and Linderholm 1958, Lambertsen et al 1959). However Wasserman et al 1967 does not find any significant change in pH during moderate exercise.

In most of the findings there is also general agreement that the arterial gas tensions and pH of the arterial blood does not show any change in the first half minute from rest to the beginning of exercise.

Effect of body temperature on exercise ventilation

There is a rise in body core temperature with exercise, the magnitude of the increase increasing with increase in work load. Whipp and Wasserman 1970, showed that with a change in body temperature (from normothermic to hypothermic, difference of 1.1°C) at the beginnings of progressive exercise tests, there were no differences in pulmonary ventilation dependent on levels of body temperature. This suggests that during exercise body temperature is not an independent stimulus to ventilation. $\dot{V}O_2$, $\dot{V}CO_2$ and $\dot{V}E$ were found to be not significantly different during the two temperature experiments doing the same work load. They also found that there was no correlation between $\dot{V}E/\dot{V}CO_2$ during exercise and temperature over a rectal temperature range of 3°C.

Petersen and Christensen 1973, suggested that hyperthermia by itself or acting with other stimuli might be an additional ventilatory drive in moderate load exercise at body temperature range of 35.5°C to 37.8°C, both $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ is constant for different loads. However, with hyperthermia at 38.5°C, both $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ were higher compared with normothermia, (as a result of decreased $\dot{V}O_2$ and $\dot{V}CO_2$ with hyperthermia, $\dot{V}E$ remaining about constant at the same work load), suggesting that the body threshold to be

near 38°C, above which hyperventilation is seen.

Grodins 1950, regarded temperature as a separate stimulus which is additive to the other stimulus. Cotes 1955, also suggested that temperature in exercise has an additive effect.

Cunningham and ÓRiordan 1957, showed that by rising body temperature by 1°C, ventilation and the ventilatory response to CO_2 increases. When core body temperature rises, at rest by 1°C, ventilation begins to rise (Barltrop 1954).

Holmgren and McIlroy 1964, found that in an experiment of stepwise increase of load up to an average load of 1200 kpm/min. and lasting about 30 minutes, the average rise in blood temperature was 1°C (range 0.2°C to 1.6°C). In moderate exercise, since there is a smaller increase in core body temperature,(about 0.3°C to 0.4°C) for this to be effective stimulus, the thermoventilatory sensing mechanism must increase its sensitivity with exercise. By increasing the core body temperature by 0.9°C (from 37.3°C to 38.2°C), Henry and Bainton 1974, showed that there is no change in ventilation, suggesting that core body temperature increase does not contribute to the hyperpnea during moderate exercise.

The time profile of temperature increase does not support the contribution of temperature as an independent stimulus to ventilation in moderate exercise. The pulmonary ventilation becomes stable after a few minutes

whereas body temperature continues to rise to a stable level after about 30 minutes (Robinson 1963).

It can be seen that in mild to moderate exercise, body temperature seems not to be an effective factor in exercise hyperpnea. However, in prolonged and heavy exercise, temperature increase is a true stimulus contributing to exercise hyperpnea. The temperature threshold of 38°C (Petersen and Christensen 1973) seems quite artificial, thus in its natural form, the effect of temperature in exercise hyperpnea is not so abruptly divided.

In this study, measurement of body temperature is not made. Since the study is conducted in a room with a controlled constant temperature, (23°C to 26°C) there is no great variation of surrounding temperature. There is wide agreement that during moderate exercise, there is no significant increase in core body temperature to affect ventilation. As measurements of the exercise slopes in this study is done only at mild to moderate exercise, it can safely be assumed that core temperature would not affect the exercise response slopes. Similarly there is no significant increase in temperature during the hypercapnic and hypoxic drive tests, thus not effecting the respective results.

Correction for lung size in CO_2 rebreathing test.

Rebuck et al., 1974, suggested that the interindividual variations in CO_2 response may be due to body

size as reflected by vital capacity. When ventilatory response was expressed in % VC/min per mm Hg PCO_2, the range of ventilatory response was reduced by 50%. Lyall and Cameron 1974, found a positive correlation between vital capacity and responsiveness towards CO_2. However Patrick and Howard 1972, did not find any correlation between the two.

In this study, vital capacity was not correlated with responsiveness to CO_2 as well as response towards exercise (expressed both as CO_2 produced and O_2 uptake). However, "correction" for vital capacity or "lung size" for CO_2 response was done to see if there was still a significant relationship between "S" and exercise response.

After correction for "lung size", there was still a significant correlation between "S" and exercise response, but there was no improvement in the correlation coefficient value.

The findings that there is no correlation between lung size as expressed by vital capacity and exercise response shows that the responses shown in the subjects is not due variations in lung size. In other words, the higher or lower response to CO_2 and exercise is not due to lung size.

Similarly there was no correlation between "S" and exercise response with body weight.

Maximum oxygen uptake: $\dot{V}O_2$ max.

Maximum uptake of oxygen, expressed in litres per

minute, is a measurement of the maximal aerobic power of an individual (or the maximal rate of aerobic energy liberation) during physical work breathing air at sea level. In other words it is the highest oxygen uptake an individual can attain doing physical work. It is a measure of the functional capacity of the respiratory and circulatory systems (Taylor et al., 1955, Saltin et al., 1968). Since for every litre of oxygen consumed in combustion, 4.7 to 5.05 kilograms calories are liberated, during work, measurement of the oxygen uptake estimates the amount of aerobic energy transfer. The higher the maximal oxygen transport, (maximal aerobic power) the greater the potential energy output. A higher oxygen transport capacity also means that a given energy output can be achieved with relatively less physiological strain. Thus it is often used as an index of physical fitness.

Amongst the many studies carried out, there are wide variations in $\dot{V}O_2$ maximum between groups as well as between individuals in different countries (Irma Astrand 1960, Cumming: 1967, Ekblom and Gjessing 1968, Ikai and Kitagawa 1972, Lars-Hermansen 1973). It is found that athletes or trained subjects show a higher $\dot{V}O_2$ max. than an untrained individual, (Astrand and Christensen 1964, Byrne-Quinn et al., 1971, Lars-Hermansen 1973). Within individuals $\dot{V}O_2$ max. increases with age, reaching maximum value at an average of 20 to

25 years, then declines (Astrand and Christensen 1964, Mitchell et al., 1958, Lars-Hermansen 1973).

The measurement of maximal oxygen uptake during various sporting activities have been studied by several workers. $\dot{V}O_2$ max. has been found to be consistently higher doing bicycle ergometer compared to treadmill exercise (either walking or running) (Faulkner et al., 1971, Hermansen et al., 1969). This may be due to the greater use of large muscle groups in treadmill than in cycling. Even in treadmill exercise, Stamford 1975 found that $\dot{V}O_2$ max. for walking significantly was lower than for running.

In this study, it was found that the $\dot{V}O_2$ max. for the trained subjects to be significantly higher than for the untrained subjects. Since there is a difficulty in obtaining a group of similarly trained subjects, subjects undergoing different types of training were chosen. Thus in this study, there were 6 marathon runners, 2 weightlifters and 2 highly trained in various sports (football and rugby). The fact that they all exhibit significantly higher $\dot{V}O_2$ max. shows that they were quite fit during the study.

However, it has been shown that training does increase an individual's $\dot{V}O_2$ max. as shown by Kearney et al., 1976. In a study of sedentary college women, there is an increase in $\dot{V}O_2$ max. with training. The training was done at two different intensities, and

it was also shown that at lower training intensity, the $\dot{V}O_2$ max. increase was lower than at higher intensity training. Conversely bed-rest has shown to decrease $\dot{V}O_2$ max. (Saltin et al., 1968, Taylor et al., 1949, Stremel et al., 1976).

Thus an athlete's performance is probably genetically controlled, but whether they show a lower CO_2 response (Byrne-Quinn et al., 1971) due to prolonged training or to genetics is not known. Whether $\dot{V}O_2$ max. used as a "fitness index" is due to genetic factor is still unknown, but training by a normal would only increase his $\dot{V}O_2$ max. at the most by 20% (Astrand and Rodahl 1970).

Prediction of $\dot{V}O_2$ max.

The use of prediction of VO_2 max. from submaximal exercise have been widely used (Astrand and Rhyming 1954, Margaria et al., 1965, and Von Doeblen 1967). Errors are small when compared with actual measurements made from maximum work. Margaria et al., 1965, in step-exercise, predicted $\dot{V}O_2$ max. using a nomogram and found $\pm$ 7% variability in their results. Von Doeblen et al., 1967 found a 10% error in their studies.

The study was done using progressive exercise and the subjects asked to continue as long as possible. This would result in some subjects with motivation to continue until maximum effort, whereas others would stop without reaching maximum work. Thus it is not possible to know the $\dot{V}O_2$ at maximum work for all the 47 subjects. Thus it is necessary to predict $\dot{V}O_2$ max.

from submaximal work using ASTRAND and ASTRAND $\dot{V}O_2$ MAX PREDICTION TABLE from SUBMAXIMAL WORK (Appendix I). To use this table the assumption made must be that the maximum heart rate is from 190 to 200 beats per minute. Correction must be made for age, but since the 47 subjects range from 18 years to 28 years old, there is no corrections needed for age. There is an error of 10% using this method (Astrand and Rodahl 1970) when compared with actual $\dot{V}O_2$ max. obtained from maximum work.

The prediction table shows $\dot{V}O_2$ max. when work load is related to heart rate and vice versa. Since there are numerous values which can be obtained, a standardised method is used. The heart rate used is between 165 beats/min. to 170 beats/min. and the corresponding nearest load obtained in the study is taken to get the VO_2 max. Corrections for body weight are made using the table in Appendix II.

Sensitivity to hypercapnia and hypoxia with exercise response.

a) Response to CO_2 at rest and exercise response.

In this study it is found that, in all the 47 normals, those showing a higher sensitivity to carbon dioxide rebreathing at rest also shows a higher ventilatory response to exercise as measured by CO_2 output and O_2 uptake. Thus in this study, Rebuck et al's 1972 results have been confirmed in a larger group of people. The 47 normals consist of 10 well-trained subjects (still undergoing training) and 37 healthy

men, not undergoing training or having any previous training. Within the group of untrained subjects, as well as in the trained subjects this relationship of those having greatest response to CO_2 showing greatest response to exercise, also stands. It is also found that the trained subjects showed a significantly lower response to CO_2 rebreathing than in untrained. ($p=<0.001$). The response to exercise, when exercise is expressed in both VO_2 and VCO_2, is also significantly lower in the trained than the untrained subjects. There are also significant negative correlations between $\dot{V}O_2$ max. and CO_2 response and between $\dot{V}O_2$ max. and exercise response. These findings are in accordance to that of Spiro et al., 1974 who suggested that the linear part of the slope of $\Delta \dot{V}_E/\Delta \dot{V}O_2$ could be an index of physical fitness. Since the linear part of $\Delta \dot{V}_E/\Delta \dot{V}CO_2$ slope follows closely to that of $\Delta \dot{V}_E/\Delta \dot{V}O_2$, this fitness index can be applied to $\Delta \dot{V}_E/\Delta \dot{V}CO_2$ too.

Matell 1963, showed that there was a fall in pH, a slight increase in $PaCO_2$ and an unchanged O_2 saturation (hence arterial PCO_2) of the blood during moderate exercise. The same subjects underwent CO_2 breathing experiments at rest. Apart from the very fast increase in ventilation during the first 30 seconds of exercise (the fast component), he showed that the slow rise (the slow component) in ventilation can be accounted for by a corresponding rise in (H^+). This relationship of

ventilation rise and (H^+) increase is similar to the one obtained during CO_2 breathing at rest. He concluded that the whole part of the slope component of exercise can be accounted for the increase in (H^+).

Dejours 1964, measured the blood PCO_2 and pH during moderate exercise and found that the fall in pH is greater than that expected from the $PaCO_2$ increases observed. This is in accordance with Matell's 1963 findings.

Cunningham 1963 used data from other workers to calculate the role of chemical contribution towards exercise. He calculated the average values of pH and $PaCO_2$ from various workers to see what would happen to ventilation if these average values were to be theoretically transfused into resting man. He found that these chemical factors contribute to only 60% of exercise ventilation. Even though corrections were made for body temperature, subjects doing different types of exercise and sitting or lying at different positions, there is still a wide variation in his subjects' response to exercise as well as their response to CO_2 at rest. The ventilatory response to CO_2 in these subjects (range 1.5 to 7.0 L min^{-1} mm Hg^{-1} CO_2 with a mean value of 4)is still higher than reported in most studies).

In progressive load experiment leading to a maximum and prolonged steady work lasting about 50 minutes, Davies et al., 1965, found that the chemical contribution to exercise hyperpnea become less as the exercise

gets longer. As the exercise takes a long time to complete, the effect of body temperature (Holmgren and McIlroy 1964, Petersen and Christensen 1973) and body catecholamine output may play a part in the hypernea (Cunningham et al., 1963$_b$, Heistad et al., 1972, Keltz et al., 1972), especially towards the later part.

b) Response to hypoxia at rest and exercise response.

In this study, 10 normals (untrained) were studied for their response to oxygen lack. There is good correlation found between hypoxia and response towards exercise, those showing the lowest response to hypoxia also shows lower response to exercise. There is also a significant negative correlation between $\dot{V}O_2$ max. and hypoxic drive. There is no study here done to see the hypoxic response in athletes. However, since there is an overlapping of $\dot{V}O_2$ max. in these 10 untrained with that of the trained, it can be seen that those undergoing the hypoxic test had a varying degree of fitness. Since $\dot{V}O_2$ max. is taken as an index of fitness, it can also be said that those who are fitter also shows a lower response to hypoxia. Similar findings by Byrne-Quinn et al., 1971, has shown that there is a significantly lower hypoxic response at rest in athletes (who had significantly higher $\dot{V}O_2$ max. than controls) compared to controls (non-athletes) at rest.

The lower response to hypoxia has been demonstrated in high-altitude inhabitants by several workers (Chiodi 1957, Weil et al., 1971, Severinghaus et al., 1966). These high-altitude inhabitants too show a lower pot-

entiation of hypoxic drive during exercise when compared to sea-level dwellers.

Hypoxia drive in exercise.

The presence of hypoxia drive during exercise in man is shown when ventilation decrease as O_2 is administered during exercise (Bannister and Cunningham 1954, Asmussen and Nielsen 1946) more so with increasing intensity. The reaction is so rapid that an effect via the chemoreceptors in the carotid and aortid bodies is assumed, with the contribution to ventilation about 12 to 20% (Dejours 1959). The threshold which this occurs is above PaO_2-200 mm.Hg. (Cunningham 1963, Kozlowski et al 1971). This occurs despite the fact that PaO_2 remains at a constant normal level during exercise.

The presence of lower hypoxic response thus diminished chemoreceptor function in trained subjects compared to untrained was shown by Briggs 1920, who found that with pure O_2 inhalation, the trained subjects' reduction in ventilation is lower than that of the untrained.

It has been shown that the ventilatory response to hypoxia is enhanced by exercise in both acute and chronic hypoxia (Pugh et al 1964 and Cunningham et al 1968) and in acute hypoxia by Weil et al 1972, and more so with increasing intensity. The peripheral arterial chemoreceptors are enhanced such that they

respond more to a given level of oxygenation than at rest.

Byrne-Quinn et al., 1971, has shown that athletes (who have significantly lower hypoxic drive than in controls), and normals showed the same magnitude of increase in hypoxic drive during exercise. This also suggests that the low hypoxic responders have the same magnitude of peripheral chemoreceptor enhancement during exercise as the high hypoxic responders. Biscoe and Purves 1967, have shown that with passive exercise in cats in normoxia, there is an increase in carotid body activity. Thus it is postulated that during exercise there is an increase in carotid body activity or an increase in "gain" of the central integrating mechanism (Byrne-Quinn et al., 1971).

Ventilatory response to CO_2 during exercise.

Asmussen and Neilsen 1957, found that there is no significant change in slope of ventilatory response to CO_2 during rest and exercise. However, there is a shift towards the left in exercise Clark and Godfrey 1969 found a small decrease in CO_2 response in steady-state exercise when compared to rest, but suggested that in their proposed model, there is no change in CO_2 sensitivity in exercise. However, Cunningham et al., 1963_a and Weil et al., 1972, have shown that there is a significant increase in CO_2 response during progressive exercise when compared to rest, the increase becoming more significant with increase in exercise intensity.

At present, it is very difficult to say whether there is augmentation of CO_2 response in exercise or not. However, the significant results of Cunningham et al., 1963a and Weil et al., 1972 weighs favourably on enhanced response to CO_2 during exercise.

Response to CO_2 at rest in trained subjects.

In this study, the 10 trained subjects showed a significantly lower CO_2 response when compared with the 37 untrained. Similar findings have been reported by Rebuck and Read 1971, Byrne-Quinn et al., 1971 and Leitch et al., 1975. The main problem is whether it is a hereditary factor or as a result of prolonged training. Leitch et al., 1975, measured the CO_2 response in a pair of identical twin athletes who were undergoing similar intensive training. They found that both had similar low ventilatory response to CO_2; when compared with non-athletes, their CO_2 response was lower.

Saunders et al., 1976 in a study of teenage swimmers, found a strong relationship between $\Delta V_E/\Delta PaCO_2$ in siblings in the same family which was independent of age, sex or training. Even though environmental factors are common, the findings that there was no correlation between these CO_2 responses and that of the father, but with that of their mother, suggested that genetic factors may be important.

Circumstantial evidence for comparison with athletes are discussed below to show whether CO_2 responsiveness is genetically acquired or could be acquired through

prolonged exposure to CO_2.

Arkinstall et al., 1974, in a study of 17 pairs of monozygous and 13 pairs of dizygous twins, showed that there is no significant difference in the intrapair variance of ventilatory response to CO_2 between the two groups. (The intrapair variance between the groups was used to estimate the contributions of hereditary and environmental factors contribution to CO_2 response). They concluded that the variability in the CO_2 response can be attributed to environmental rather than genetic factors. This variability between twins was due to frequency response (which was due to personality factors) and tidal volume response which was largely determined by genetic factor.

The findings of Beral and Read 1971 of a low ventilatory response to CO_2 in the Engas in New Guinea and the lower variability of response between individuals when compared to that of healthy Caucasians, led them to suggest that genetic and racial factors account for the marked variability of the ventilatory response to CO_2 in normal man.

The two major factors which determine a subject's ventilatory response to CO_2 are the tidal volume response (Rebuck et al., 1974) and lung size (Cross et al., 1953, Rebuck et al., 1974, Lyall and Cameron 1974). It was shown by Arkinstall et al., 1974, that the tidal volume response is largely genetic in nature. In addition, lung volume, as expressed by vital capacity, is influenced by genetic factors, (Arkinstall et al., 1974). Thus

genetic factors are important in the determination of one's CO_2 response.

However, lowered CO_2 response can also be attributed to constant prolonged exposure to high PCO_2. Schaefer 1955, in a study of submarine escape tank instructors (essentially breath-hold divers), found their CO_2 responsiveness to be lower than non-divers. However, in another study, Schaefer 1965 found that the CO_2 responsiveness returned towards normal when the divers did not do any diving for some months, but returned to a low CO_2 response when diving resumed. Song et al.,1963, found that diving women in Korea have a lower CO_2 response than normals. Similarly, Lally et. al.1974, reported a low ventilatory response to exercise which they suggested as due to lower CO_2 response, in divers. From these facts it can be assumed that intensive breath-holding does induce reduced chemosensitivity to CO_2.

'Anaerobic threshold' in exercise ventilatory response slopes.

From Tables 2-3a and 2-3b, it can be seen that in the 2 non-trained amd 2 trained subjects chosen as representative, the VO_2 is quite similar at similar loads. This was true for all the 47 subjects studied. The only difference between the trained and untrained subjects was the load at which $\Delta\dot{V}E/\Delta\dot{V}O_2$ and $\Delta\dot{V}E/\Delta\dot{V}CO_2$ relationships become non-linear (Table 2-5). This load in the table is the 'Load Limit'.

There is a significant difference ($p=\leqslant 0.001$) of the point where there is a break in linearity in the ven-

tilatory response slopes ('anaerobic threshold') in trained and untrained subjects. The break occurs at lower loads in the non-trained subjects when compared with the trained. This is in accordance with the findings of Wasserman et al., 1973 who found in normals between 17 years and 91 years old, the anaerobic threshold to vary from 45 watt or 270 kpm/min. ($\dot{V}O_2$=1 L/min) to very fit adults of up to a maximum of 180 watt (1050 kpm/min). In this study, there is a range of "fitness" in the untrained and the range of load at which this "break" occurs range from 700 kpm/min. to 1100 kpm/min. In the trained subjects this "break" occurs in a narrow range of 1100 to 1200 kpm/min. Since it is difficult to say at which load is the maximum work done, this "anaerobic threshold" cannot be quantitated in terms of % maximum work.

However, from the predicted $\dot{V}O_2$ max., it is possible to express (from $\dot{V}O_2$ at which load this AT occurs) the % of maximum oxygen uptake where AT occurs. It has been found that this ranges from 65 to 75% of aerobic capacity, thus in general agreeing with the findings of this study.

When $\dot{V}O_2$ at which anaerobic threshold occurs is expressed as % of $\dot{V}O_2$ max. there is a range of between 56% to 90%. There is no significant difference between the trained and the untrained as far as this % is concerned; (untrained-mean 72.4, SD 8.6; trained-mean 77.19, SD 5.95). Only 8 subjects (1 trained and 7 untrained) out of 47 subjects have a value of 80% to 90%

and 1 trained at 90%. This agrees quite well with other fidings that the anaerobic threshold is about 55% to 75% of total aerobic capacity.

From this one can see that the anaerobic threshold is at around the same percentage of VO_2 max. But this 'break' occurs at a lower absolute workload in non-trained than the trained subjects. Hermansen 1971 found similar results and Wasserman et al.,1975 suggested that this criteria may be used as a fitness index. (Fig. 2-18)

Chemosensitivity and exercise ventilation.

In this study, there was a significant correlation between response to hypoxia and to hypercapnia, suggesting related peripheral and central chemosensitivities. Significant correlations are obtained too between these chemosensitive responses and exercise ventilation. Circumstantial evidence is presented below to discuss these correlations.

It is widely known that the carotid body is responsible for the hypoxic drive in man. Lugliani et al 1974, has shown that bilateral removal of carotid body resulted in the absence of hypoxic drive. Guz et al, 1966 showed that after vagus and glossopharyngeal nerve block, 'A' is reduced. Holton and Wood 1965 showed absent hypoxic drive after glomectomy in patients. Wade et al 1970, showed that denervation of the glomus caused significant loss of hypoxic drive.

The main response to hypercapnia is mediated cen-

trally via the medullary chemoreceptors (see Section 1A). Sorensen 1971 has shown that CO_2 stimulates ventilation through its effect on both peripheral and central chemoreceptive areas. The relative contribution of each to the total ventilatory response to CO_2 is difficult to determine, however, the contribution of the peripheral chemoreceptors can be predicted from results obtained by Lambertsen et al., 1961 and Mitchell and Singer 1965. Lambertsen et al., 1961 did this by keeping the blood pH constant in his subjects by infusing alkali whilst they were undergoing CO_2 breathing. They found a 55% reduction in the CO_2 response slope when compared with controls. Assuming the effect of arterial pH to be entirely mediated by the peripheral chemoreceptors, it would suggest that in the absence of the peripheral chemoreceptor sensitivity, the CO_2 response slope would be reduced by 55% in an individual. In a single subject, Mitchell and Singer 1965, estimated that the central chemoreceptive areas to be 3.4 times as sensitive to H^+ changes than the peripheral chemoreceptors. Denervation of peripheral chemoreceptors would cause a 20% decrease in CO_2 response slope in his subject if no compensatory changes occur. This leads Sorensen and Severinghaus 1968 to conclude that 20% to 55% of the ventilatory response to CO_2 is mediated via the peripheral chemoreceptive areas. Byrne-Quinn et al., 1971 also obtained this magnitude of ventilatory reduction in CO_2 response in his athletes compared to his normal control. In this study, the trained subjects show a

mean reduction of 44% in CO_2 response compared with that of the untrained subjects.

The information carried by afferent fibres from the carotid body has been shown to be both hypercapnic and hypoxic in nature. This was done from single afferent fibre preparations from the carotid body by Biscoe et al., 1969. The relationship of reduced "S" and "A", was shown by Sorensen and Severinghaus 1968 in high altitude natives who have reduced hypoxic drive showed a reduced response to a single breath of CO_2 suggesting diminished peripheral chemoreceptor function. In this study, it shows the diminished peripheral chemoreceptor function (thus probably medullary chemoreceptor) in athletes, when compared to the untrained, as far as CO_2 is concerned. There is also a significant correlation between response to hypercapnia and to hypoxia in this study and in Section 1A. At present one cannot say whether this alteration is in the function of carotid body itself or in the central integration of its afferent impulses.

The presence of an increased chemosensitivity during exercise was shown when the depression of ventilation produced by oxygen inhalation during exercise is greater than that when at rest (Asmussen and Neilsen 1946, Dejours 1964, Hickman et al., 1951). Weil et al., 1972 did a quantitative experiment to determine to what extent this argumentation of chemosensitivity contributes to the hypernea of exercise. Measurement of hypoxic and hypercapnic drives were made during exercise and at rest. The results show an increased CO_2 and hypoxic response, even

with mild exercise with more marked response at higher work loads. Increase in CO_2 sensitivity with exercise compared to that at rest has been reported by Hickman et al., 1951, Bannister and Cunningham 1954, Cunningham et al., 1963a. This increased chemosensitivity in exercise would partly explain for some of the 40% of ventilation left unaccounted for in Cunningham's calculation (Cunningham 1963) as well as Davies' decreased role of humoral factor in prolonged exercise.

It is not certain whether the increased chemosensitivity during exercise is due to central or peripheral causes. However, experiments by Biscoe and Purves 1967 with anaethesied cats showed an immediate increase in carotid body activity when passive exercise was performed. These enhanced carotid body activity disappears when the carotid body sympathetic nerve supply was cut, suggesting that the enhanced chemosensitivity during exercise is due to increased sympathetic nerve activity to the carotid bodies. However, experiments on patients who had bilateral carotid body removal showed that there was no enhancement of ventilation on exercise (Lugliani et al., 1971).

Weil et al., 1972, suggested that the increased sensitivity to both CO_2 and hypoxic drives in exercise when compared to resting conditions is attributable to an increased peripheral chemosensitivity. As it has been shown that athletes have lower CO_2 response than normals and during exercise the increase in ventilation

with hypoxia is the same in both groups (Byrne-Quinn et al., 1971), it would suggest that the increase in sensitivity of the peripheral chemoreceptor would be similar in both.

The findings in this study of subjects with low chemosensitivity showing low exercise ventilatory response (and those with greater chemosensitivity showing higher exercise ventilatory response) could thus be explained by the sensitivity of the peripheral chemoreceptors. If one assumes that only the central cehmoreceptive areas are enhanced by exercise, that would explain the CO_2 response and its correlation with exercise ventilatory response. The correlation shown by the response to hypoxia at rest with exercise ventilatory response does suggest involvement with enhanced carotid body activity with exercise as well.

SECTION 3

THE BREATHING PATTERN IN NORMAL SUBJECTS.

INTRODUCTION

The mechanism of regulation of breathing pattern has been analysed in several forms for many years. Hey et al., 1966 and Euler et al., 1970 studied ventilation, tidal volume and respiratory frequency or its reciprocal, and total breath duration ($T_{tot.}$).

Later the total breath duration was further subdivided and its components, inspiratory duration ($T_{insp.}$) and expiratory duration ($T_{exp.}$) was studied by various workers. Thus Clark and Euler 1972 studied the duration of inspiratory and expiratory phases in man and cats during CO_2 rebreathing. Cunningham and Gardner 1972 studied the relationship between tidal volume and mean inspiratory and expiratory times in man during steady-state CO_2 breathing. Jennett et al., 1974 studied the ~~mean~~ duration of inspiration and expiration in man during CO_2 rebreathing, early phases of exercise and steady-state hypoxia.

Rebuck et al., 1976 studied duration of breaths during progressive hypercapnia and hypoxia and Kay et al., 1975 studied both the mean and breath by breath breathing pattern in man during steady-state exercise and steady-state hypercapnia.

In this study, the breathing pattern with its components, $T_{insp.}$ (inspiratory time) $T_{exp.}$ (expiratory time), $T_{tot.}$ (total breath duration) and tidal volume were studied during CO_2 rebreathing, progressive hypoxia and progressive exercise. The data obtained was analysed

to see if there was any difference in the breathing pattern with the different ventilatory stimuli.

Methods.

This study was done in conjunction with those in Sections 1A and 2. Progressive hypercapnia, progressive hypoxia and progressive exercise tests carried out were those carried out in the previous sections. The breath duration was taken from the tracings of ventilation recorded as breath by breath tidal volume measurements.

Tidal volume measurements for the hypercapnia and hypoxia studies were of expired tidal volume whilst those for exercise studies were of inspired volume.

Treatment of data.

A typical trace for this experiment is shown in Fig.3-a.

The whole duration of the experiment was divided into 30 second intervals. 4 breaths were taken from each section and the mean tidal volume, $T_{insp.}$, $T_{exp.}$ and from these, the $T_{tot.}$ were calculated.

Irregular breaths were excluded if:

a) Tidal volume was 1.5 times that of the mean tidal volume value.

b) $T_{insp.}$ was twice that of the mean $T_{insp.}$ value.

c) Misrecording occurred (e.g. when subjects coughed, electrical resetting on electrospirometer).

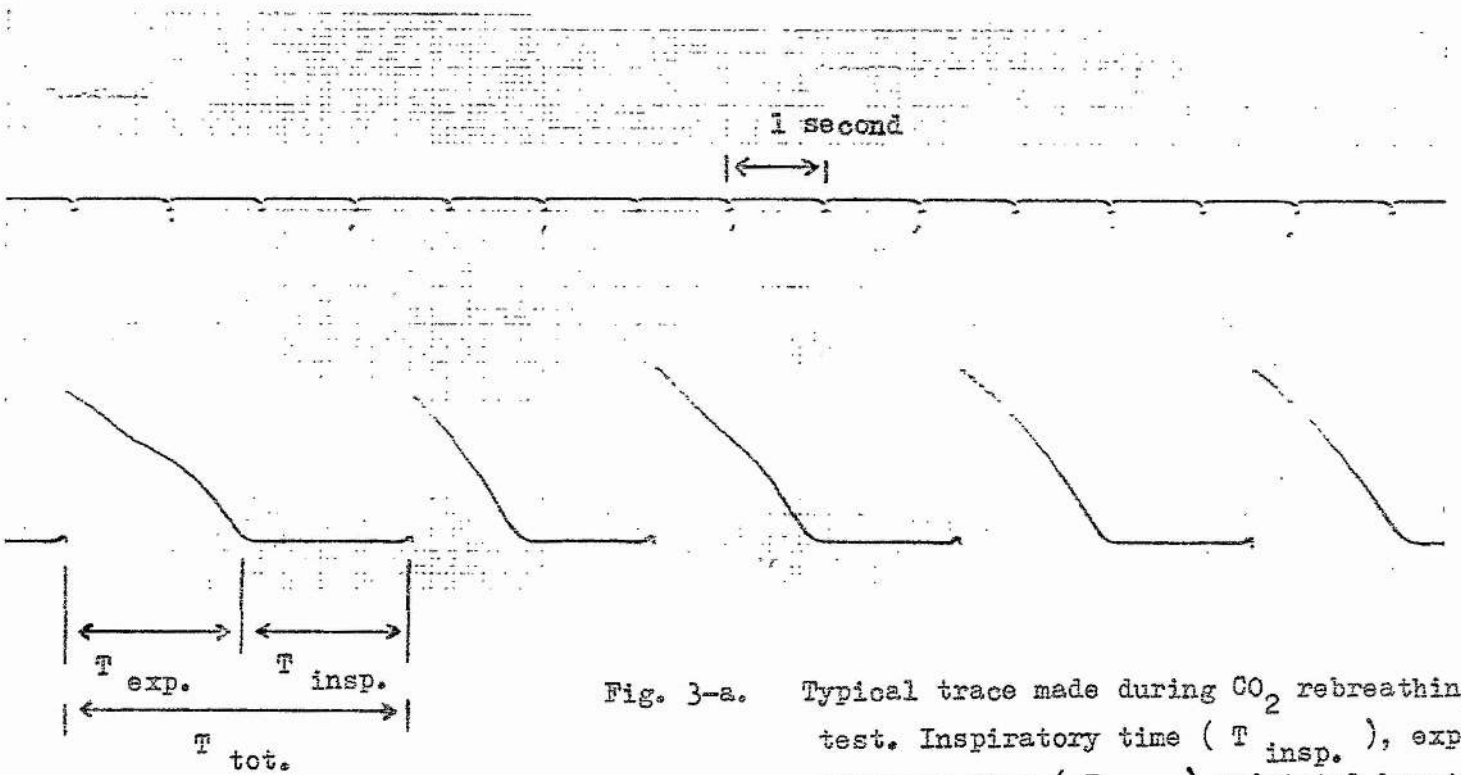


Fig. 3-a. Typical trace made during CO_2 rebreathing test. Inspiratory time ($T_{insp.}$), expiratory time ($T_{exp.}$) and total breath duration ($T_{tot.}$) measured in seconds.

RESULTS

a) Progressive hypercapnia

In all the 10 subjects studied, there was a significant progressive shortening of breath duration with increasing PCO_2. Both tidal volume (in this case expired tidal volume) and breathing frequency increased with rising PCO_2. The shortening of the total breath duration ($T_{tot.}$) was mainly due to the shortening of expiratory time ($T_{exp.}$), whilst inspiratory time ($T_{insp.}$) remained constant. There was a significant shortening of $T_{exp.}$ with increasing V_T in all the 10 subjects. In range 1, $T_{insp.}$ was constant with increasing tidal volume. (Figs. 3-1 and 3-2, Tables 3-1 and 3-2). Thus 9 subjects showed the range 1 throughout the whole duration of rebreathing. Only one subject (subject DMI) showed both range 1 and 2. In range 2, increases in tidal volume after 2.5 times eupnoeic value resulted in shortening of $T_{insp.}$ (Fig. 3-3, Table 3-3).

b) Progressive hypoxia.

All the 10 subjects studied showed shortening of breath duration with increasing tidal volume. As with progressive hypercapnia and progressive exercise, this shortening was mainly due to the significant shortening of expiratory time, with inspiratory time being constant. 9 subjects showed range 1 throughout the duration of the test. (Figs. 3-4 and 3-5, Tables

V_T	$T_{insp.}$			$T_{exp.}$			$T_{tot.}$
	mean.	SD	SE	mean.	SD	SE	
1.153	1.25	0.12	0.07	2.74	0.28	0.11	3.99
1.467	1.23	0.10	0.03	2.41	0.20	0.10	3.65
1.741	1.14	0.08	0.03	2.37	0.21	0.09	3.51
1.911	1.27	0.07	0.06	2.10	0.18	0.11	3.37
2.216	1.28	0.04	0.03	1.86	0.20	0.04	3.14
2.169	1.23	0.06	0.02	1.63	0.27	0.04	2.86
2.491	1.27	0.05	0.05	1.48	0.17	0.03	2.75
2.671	1.16	0.07	0.03	1.21	0.20	0.03	2.37
2.690	1.18	0.11	0.04	0.98	0.19	0.03	2.16

Table 3-1. Data obtained for breath duration components and tidal volume during CO_2 rebreathing in subject GD.

Note. Symbols used in Tables 3-1 to 3-9.

V_T tidal volume in litres.

$T_{insp.}$ inspiratory time in seconds.

$T_{exp.}$ expiratory time in seconds.

$T_{tot.}$ total breath duration in seconds.

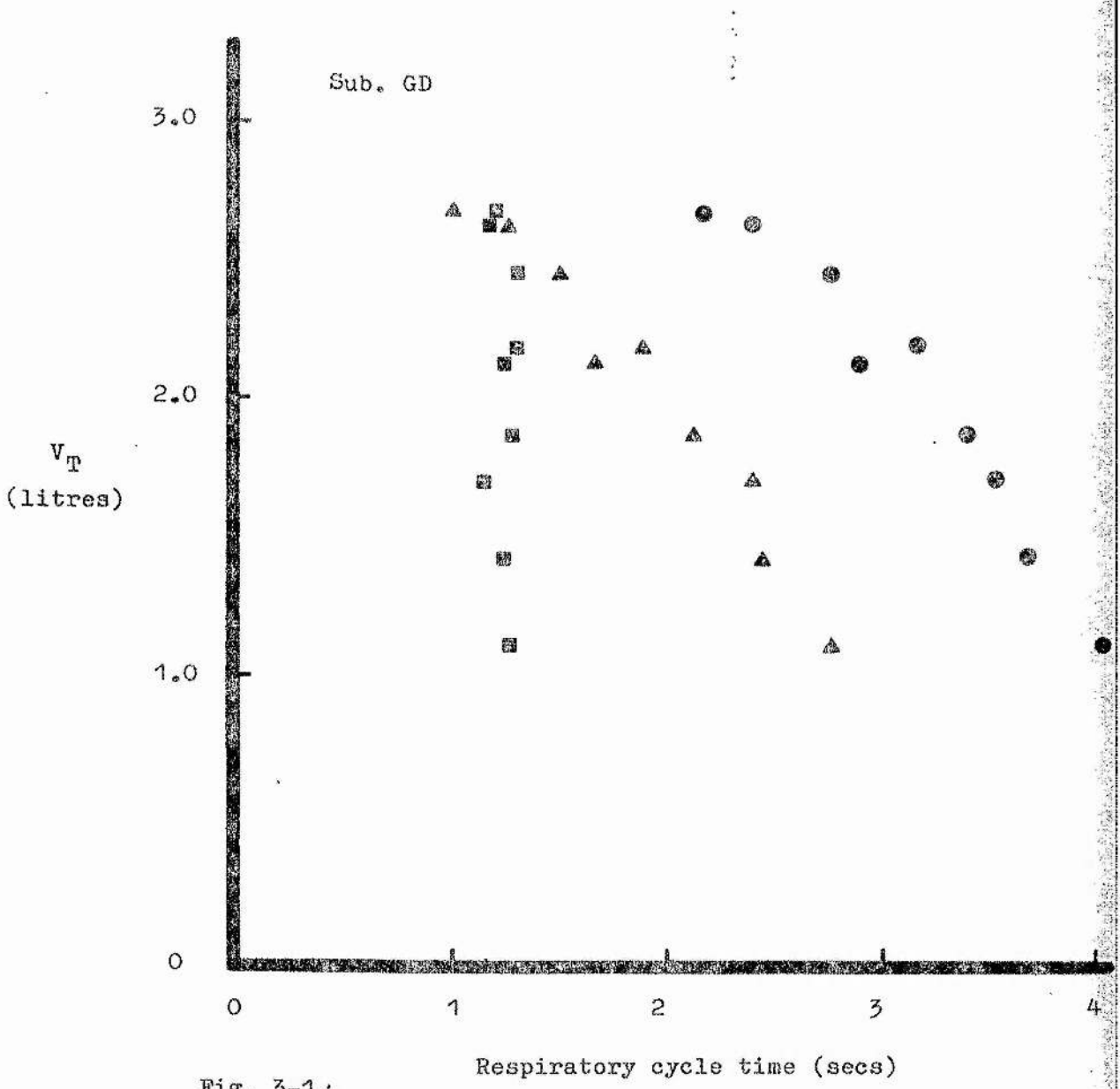


Fig. 3-1.

Tidal volume V_T plotted against respiratory cycle time during CO_2 rebreathing in one representative subject.

- ■ inspiratory time.
- ▲ expiratory time.
- ● total breath duration.

V_T	$T_{insp.}$			$T_{exp.}$			$T_{tot.}$
	mean.	SD	SE	mean.	SD	SE	
1.300	1.12	0.25	0.15	3.26	0.40	0.13	4.38
1.162	1.15	0.24	0.12	2.88	0.21	0.10	4.03
1.541	1.13	0.19	0.06	1.87	0.18	0.06	3.10
1.807	1.24	0.16	0.05	1.66	0.21	0.10	2.91
1.877	1.18	0.15	0.04	1.48	0.24	0.07	2.66
2.627	1.10	0.15	0.04	1.61	0.18	0.05	2.71
2.352	0.91	0.13	0.03	1.37	0.15	0.04	2.28
2.434	1.03	0.20	0.05	1.18	0.17	0.04	2.21
2.223	0.85	0.18	0.04	1.26	0.17	0.03	2.11
2.447	0.97	0.10	0.02	1.18	0.14	0.04	2.15

Table 3-2. Data obtained for breath duration components and tidal volume during CO_2 rebreathing in subject VE.

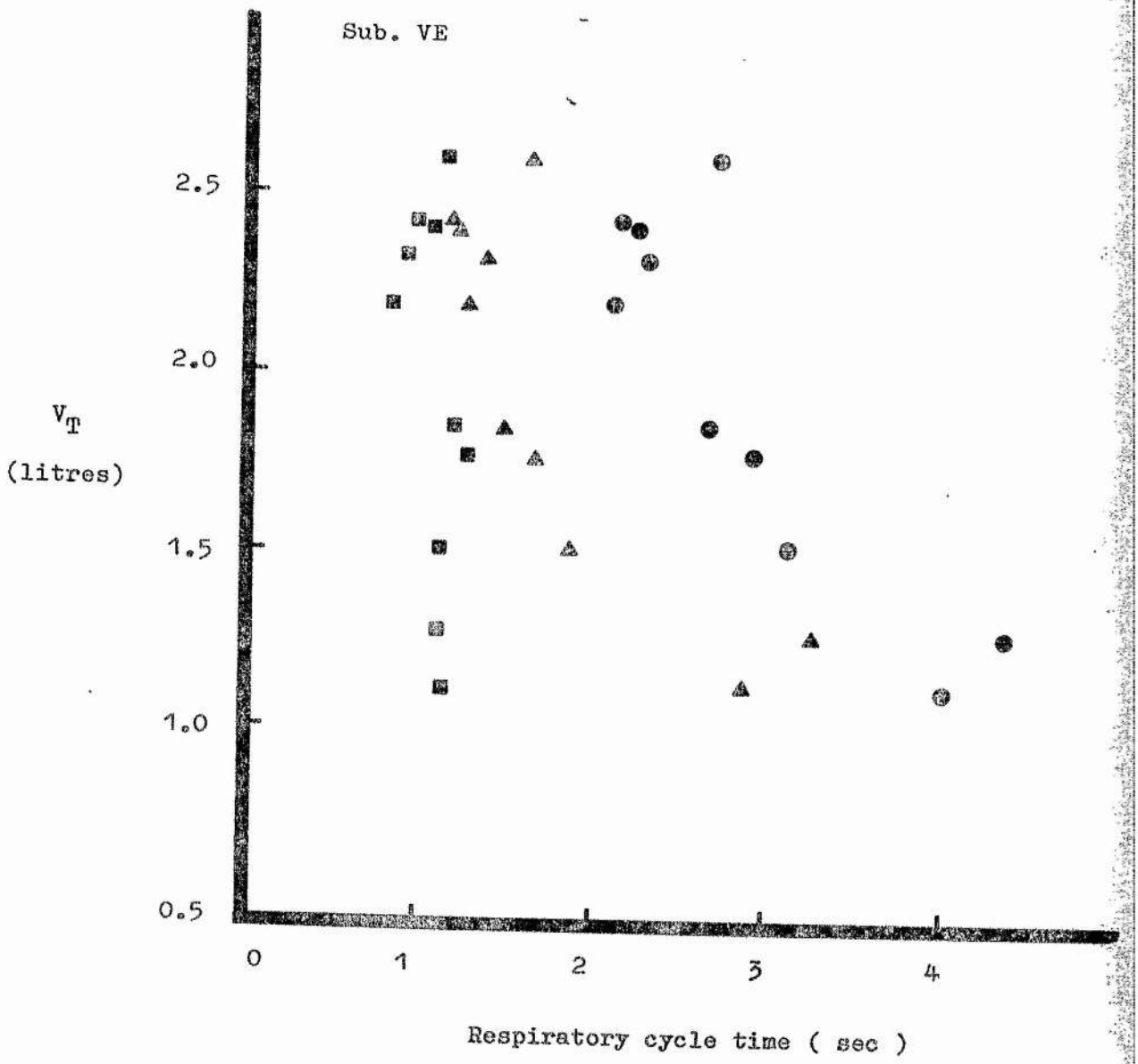


Fig. 3-2

Tidal volume V_T plotted against respiratory cycle time during CO_2 rebreathing in one representative subject.

- ■ inspiratory time.
- ▲ expiratory time.
- ● total breath duration.

V_T	$T_{insp.}$			$T_{exp.}$			$T_{tot.}$
	mean.	SD	SE	mean.	SD	SE	
0.698	1.69	0.26	0.10	2.30	0.20	0.05	3.99
0.772	1.75	0.30	0.16	2.14	0.13	0.04	3.89
0.981	1.69	0.20	0.07	2.01	0.20	0.06	3.70
1.404	1.70	0.15	0.08	1.80	0.18	0.08	3.50
1.716	1.61	0.18	0.07	1.61	0.20	0.07	3.22
2.417	1.69	0.19	0.07	1.68	0.13	0.07	3.37
2.749	1.19	0.20	0.11	1.46	0.15	0.05	2.66
2.955	1.26	0.20	0.07	1.49	0.18	0.08	2.75
3.081	1.22	0.18	0.10	1.47	0.18	0.10	2.70
3.096	1.06	0.18	0.09	1.30	0.13	0.04	2.36

Table 3-3. Data obtained for breath duration components and tidal volume during CO_2 rebreathing in subject DMI.

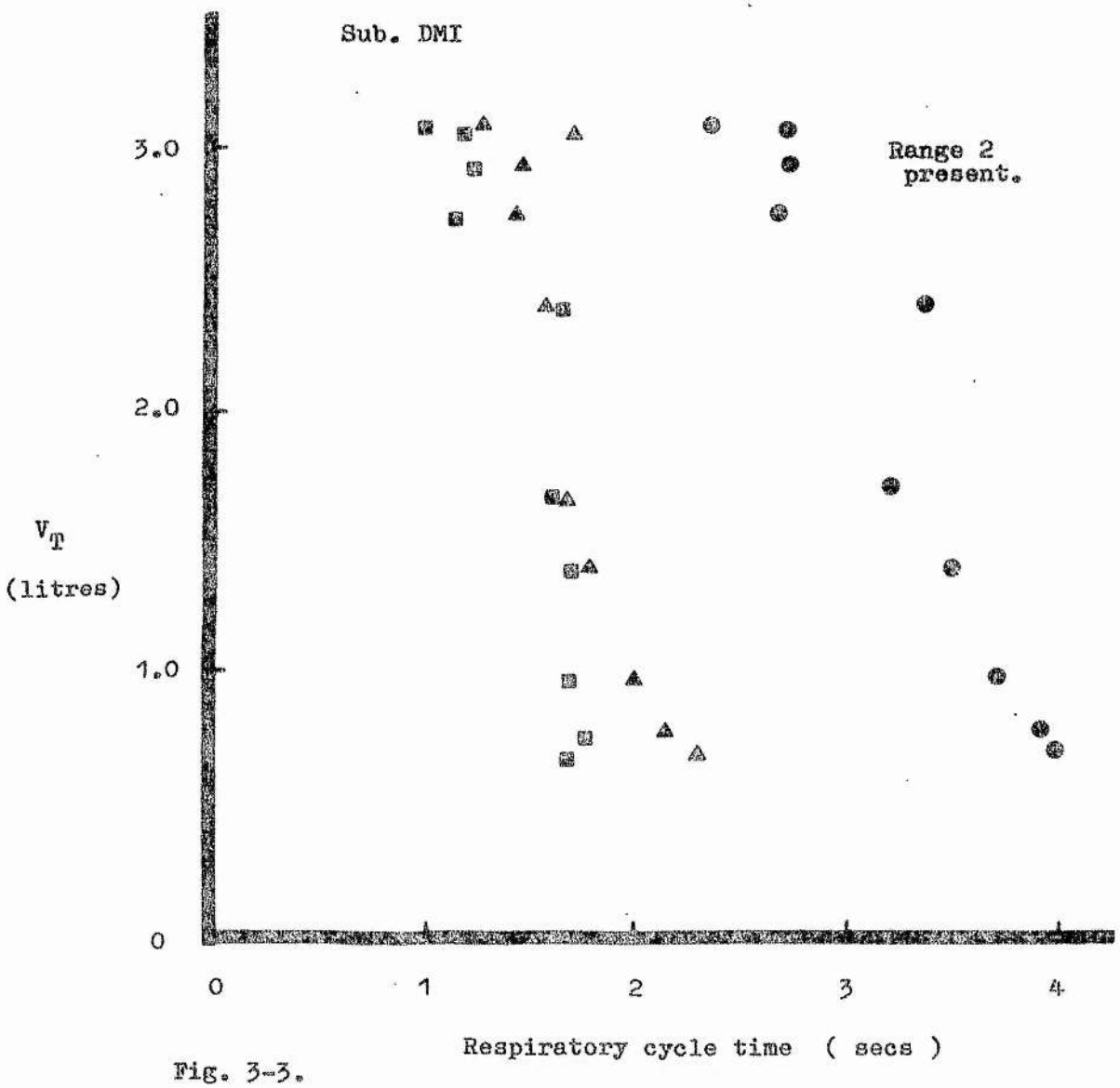


Fig. 3-3.

Tidal volume V_T plotted against respiratory cycle time during CO_2 rebreathing in one subject.

- ■ inspiratory time.
- ▲ expiratory time.
- ● total breath duration.

V_T	$T_{insp.}$			$T_{exp.}$			$T_{tot.}$
	mean.	SD	SE	mean.	SD	SE	
1.00	1.90	0.26	0.10	2.75	0.44	0.14	4.65
1.12	2.10	0.18	0.08	2.60	0.25	0.06	4.70
1.37	2.00	0.20	0.11	2.50	0.20	0.05	4.50
1.50	2.15	0.15	0.06	2.32	0.18	0.05	4.42
2.00	2.00	0.20	0.06	2.16	0.18	0.04	4.16
1.93	1.93	0.22	0.05	1.76	0.22	0.04	3.69
2.18	1.96	0.16	0.04	1.28	0.18	0.06	3.24
2.50	2.00	0.15	0.06	1.20	0.15	0.05	3.20

Table 3-4. Data obtained for breath duration components and tidal volume during progressive hypoxia in subject 3-1.

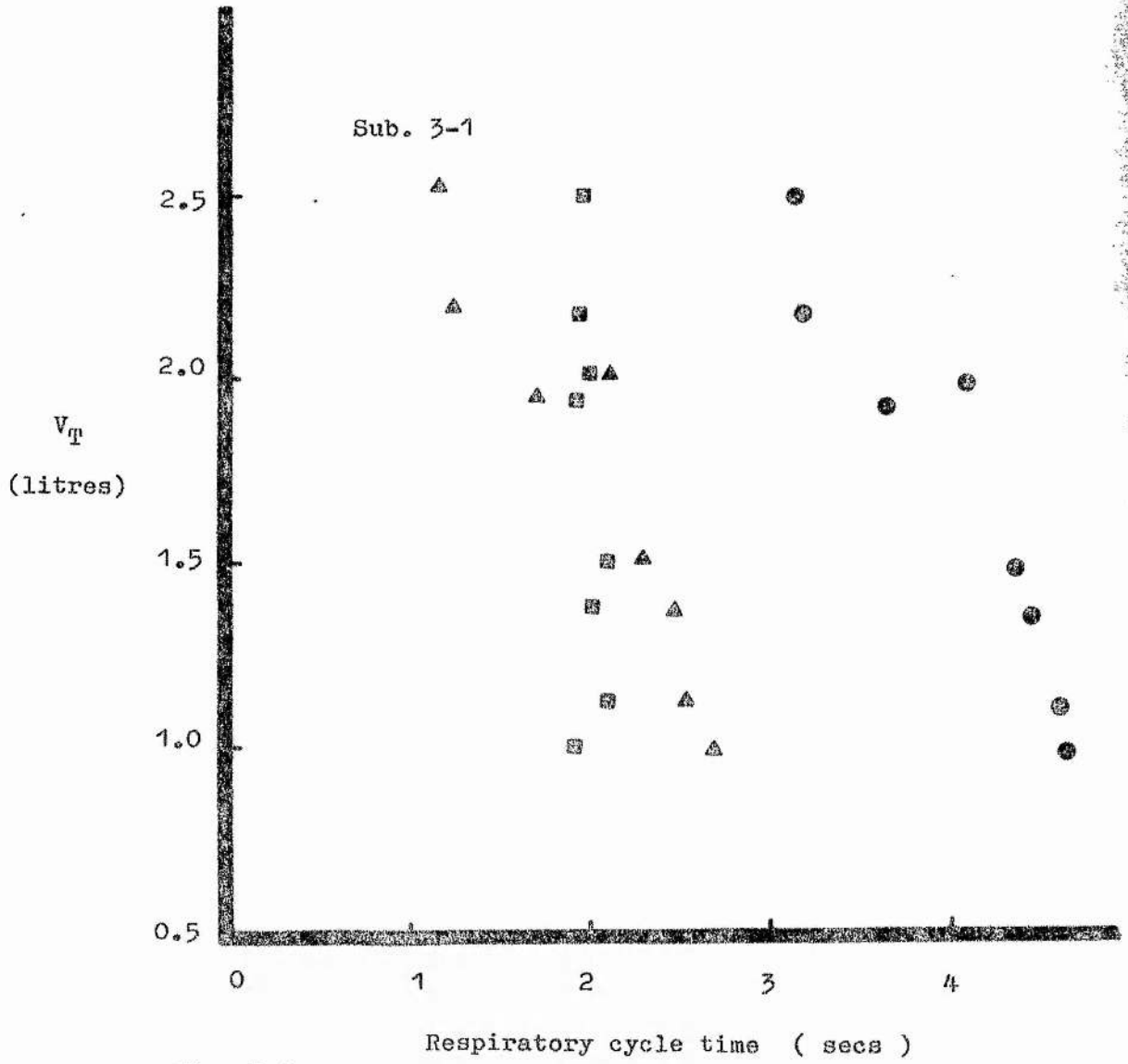


Fig. 3-4.

Tidal volume V_T plotted against respiratory cycle time during progressive hypoxia in one representative subject.

- ■ inspiratory time.
- ▲ expiratory time.
- ● total breath duration.

V_T	$T_{insp.}$			$T_{exp.}$			$T_{tot.}$
	mean.	SD	SE	mean.	SD	SE	
1.37	2.64	0.35	0.11	2.80	0.40	0.14	5.50
1.75	2.70	0.30	0.10	2.70	0.25	0.09	5.40
2.06	2.64	0.25	0.08	2.50	0.19	0.04	5.14
2.62	2.60	0.20	0.08	2.52	0.20	0.04	5.12
2.72	2.70	0.18	0.06	2.19	0.16	0.03	4.80
2.56	2.60	0.18	0.06	2.03	0.13	0.03	4.63
3.00	2.68	0.11	0.05	1.78	0.08	0.01	4.46

Table 3-5. Data obtained for breath duration components and tidal volume during progressive hypoxia in subject 3-2.

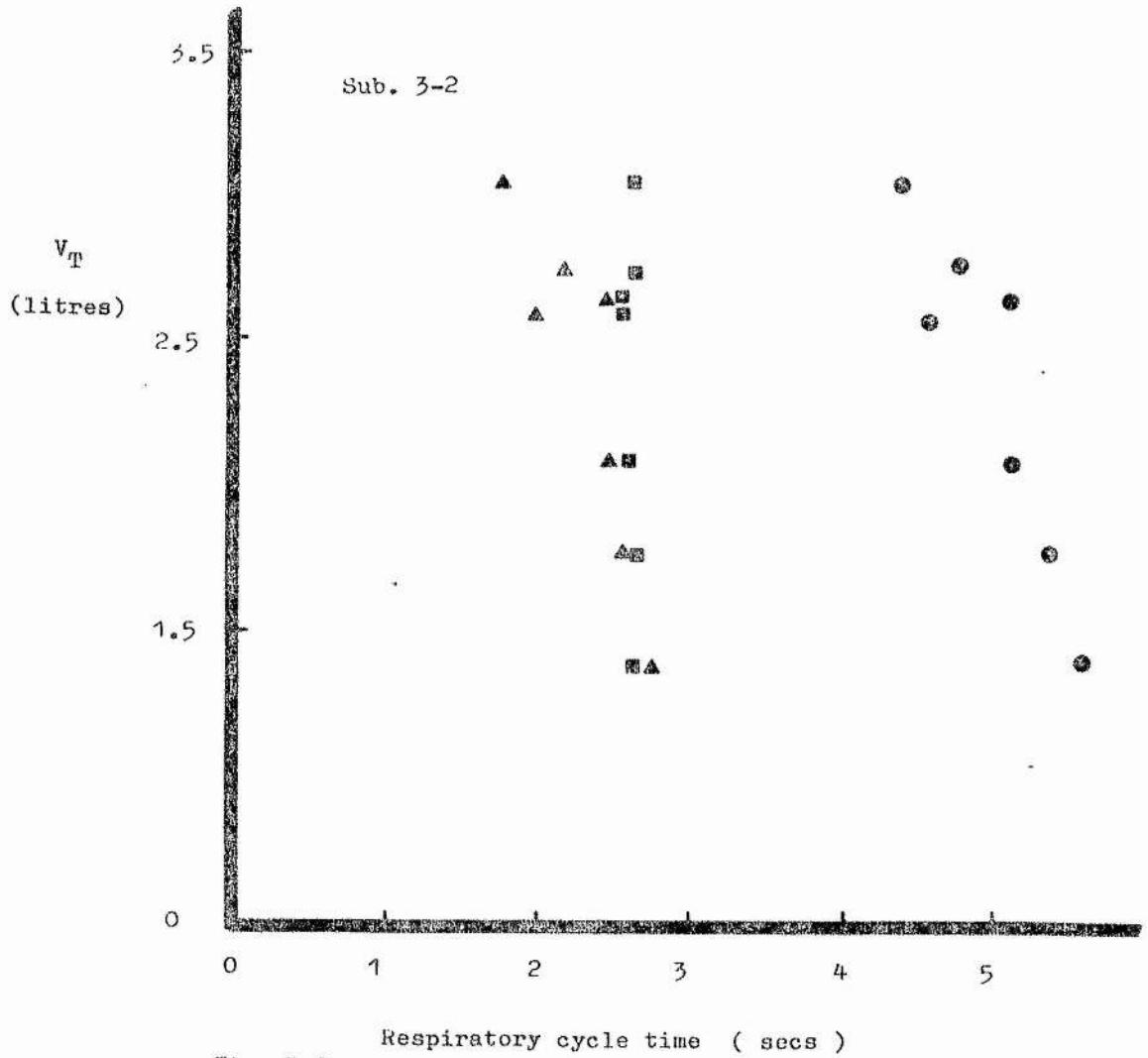


Fig. 3-5.

Tidal volume V_T plotted against respiratory cycle time during progressive hypoxia in a representative subject.

- ■ inspiratory time.
- ▲ expiratory time.
- ● total breath duration.

V_T	$T_{insp.}$			$T_{exp.}$			$T_{tot.}$
	mean.	SD	SE	mean.	SD	SE	
1.72	2.00	0.21	0.05	1.70	0.22	0.05	3.70
2.20	2.10	0.30	0.15	1.65	0.24	0.10	3.75
2.51	1.96	0.18	0.03	1.53	0.19	0.05	3.49
2.62	1.92	0.14	0.04	1.51	0.18	0.06	3.46
3.11	1.92	0.20	0.06	1.38	0.20	0.07	3.30
3.20	1.30	0.18	0.05	1.00	0.16	0.05	2.30
3.30	1.15	0.15	0.03	0.85	0.09	0.02	2.00

Table 3-6. Data obtained for breath duration components and tidal volume during progressive hypoxia in subject 3-3.

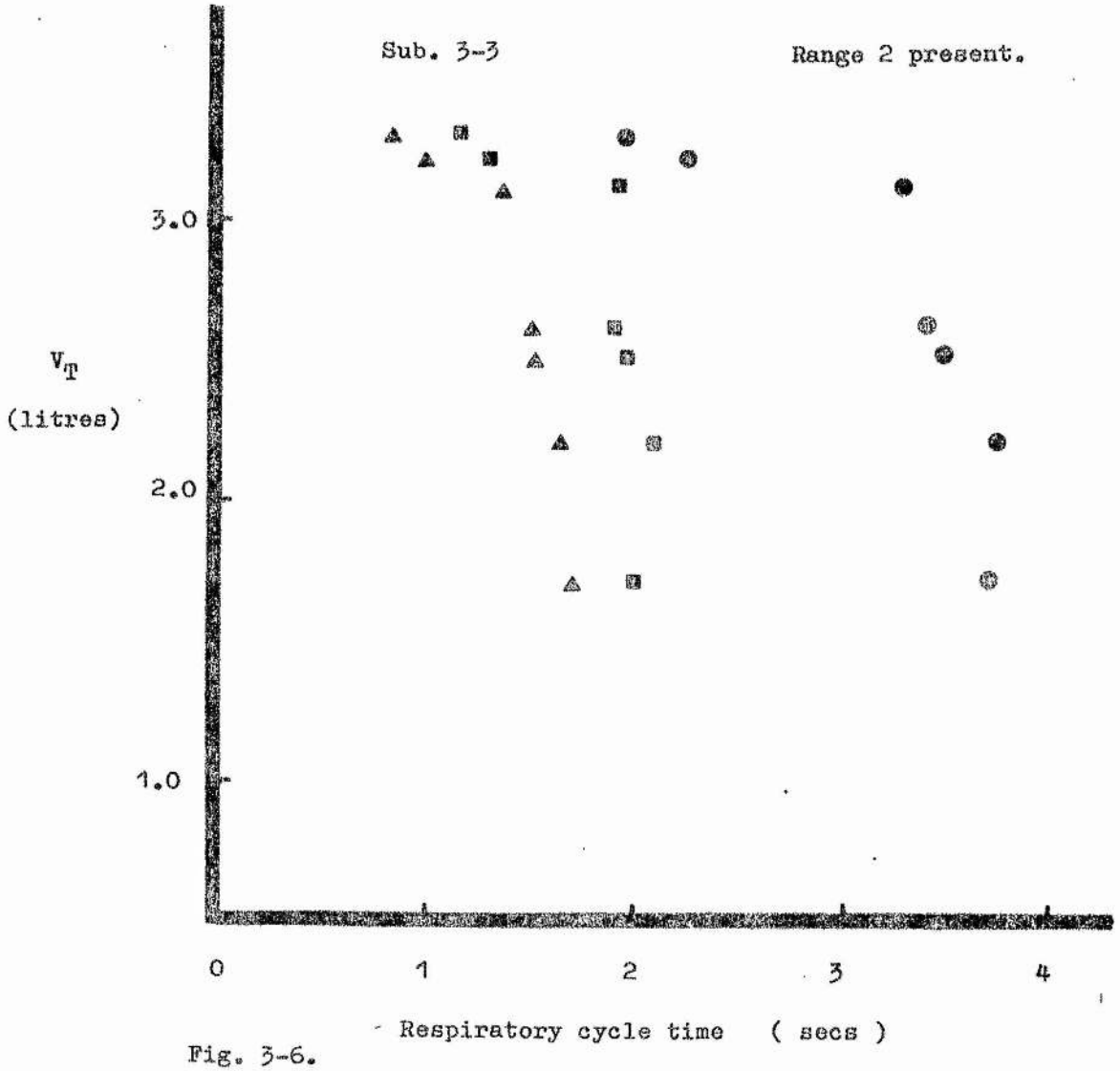


Fig. 3-6.

Tidal volume V_T plotted against respiratory cycle time during progressive hypoxia in a subject.

- ▪ inspiratory time.
- ▲ expiratory time.
- ● total breath duration.

V_T	$T_{insp.}$			$T_{exp.}$			$T_{tot.}$
	mean.	SD	SE	mean.	SD	SE	
0.623	0.84	0.07	0.02	2.41	0.23	0.09	3.25
0.882	0.81	0.15	0.05	2.00	0.19	0.06	2.82
0.936	0.78	0.18	0.09	1.88	0.32	0.11	2.66
1.022	0.83	0.19	0.06	1.67	0.25	0.09	2.50
1.192	0.84	0.11	0.03	1.44	0.30	0.08	2.29
1.207	0.75	0.15	0.05	1.04	0.17	0.05	1.79
1.398	0.78	0.12	0.05	1.16	0.20	0.10	1.94
1.424	0.72	0.09	0.02	0.98	0.21	0.09	1.70
1.473	0.71	0.06	0.02	0.86	0.07	0.02	1.58
1.618	0.78	0.05	0.01	0.68	0.10	0.02	1.46

Table 3-7. Data obtained for breath duration components and tidal volume during progressive exercise in subject SC.

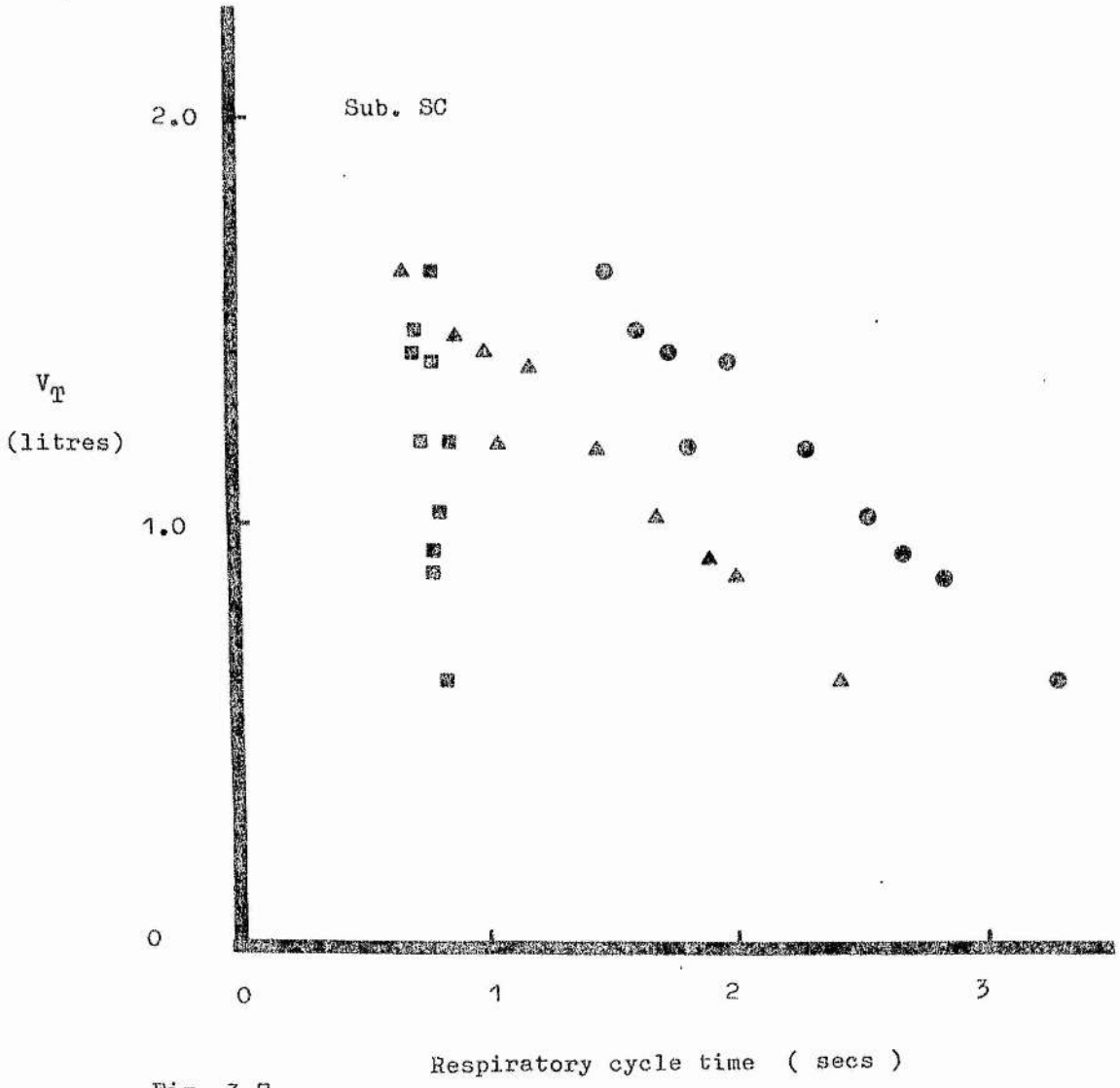


Fig. 3-7.

Tidal volume V_T plotted against respiratory cycle time during progressive exercise in one representative subject.

- ▪ inspiratory time.
- ▲ expiratory time.
- ● total breath duration.

V_T	$T_{insp.}$			$T_{exp.}$			$T_{tot.}$
	mean.	SD	SE	mean.	SD	SE	
0.574	0.75	0.07	0.01	1.61	0.20	0.04	2.36
0.936	0.74	0.06	0.01	1.40	0.09	0.02	2.14
0.974	0.78	0.08	0.01	1.30	0.11	0.02	2.08
0.985	0.77	0.05	0.01	1.20	0.11	0.02	1.97
1.090	0.73	0.08	0.01	1.12	0.10	0.02	1.85
1.123	0.72	0.08	0.01	1.10	0.10	0.02	1.82
1.247	0.68	0.04	0.02	0.95	0.13	0.02	1.63
1.400	0.68	0.06	0.01	1.07	0.19	0.04	1.75
1.562	0.66	0.05	0.01	0.91	0.09	0.02	1.57
1.599	0.67	0.11	0.01	0.86	0.10	0.02	1.54
1.675	0.76	0.12	0.03	0.67	0.06	0.01	1.43
1.980	0.67	0.11	0.03	0.43	0.11	0.04	1.10

Table 3-8. Data obtained for breath duration components and tidal volume during progressive exercise in subject FH.

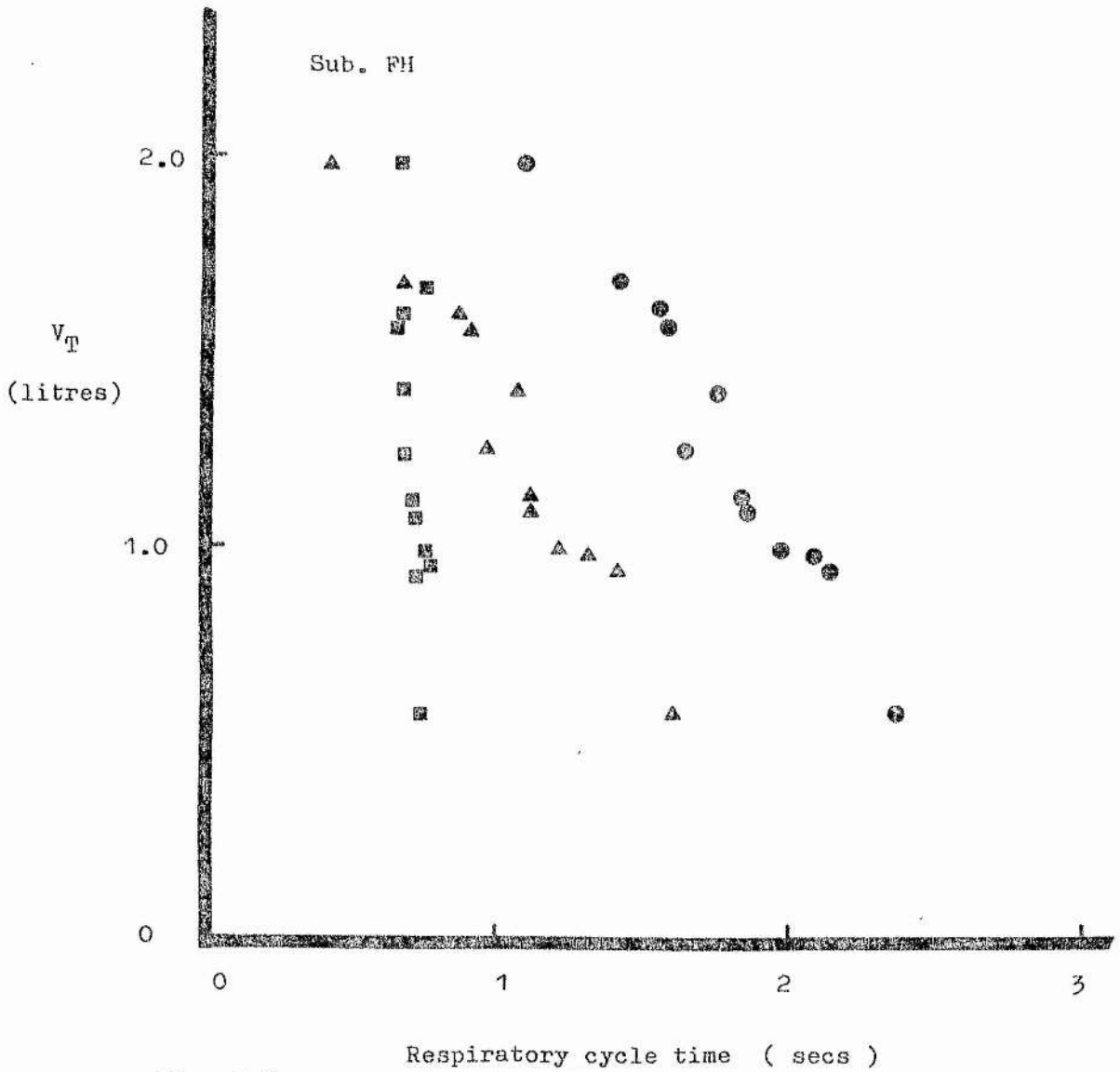


Fig. 3-8.

Tidal volume V_T plotted against respiratory cycle time during progressive exercise in one representative subject.

- ■ inspiratory time.
- ▲ expiratory time.
- ● total breath duration.

V_T	$T_{insp.}$			$T_{exp.}$			$T_{tot.}$
	mean.	SD	SE	mean.	SD	SE	
0.726	1.10	0.25	0.07	2.33	0.58	0.16	3.43
0.902	1.07	0.10	0.02	1.90	0.20	0.06	2.96
1.042	1.04	0.14	0.04	1.73	0.27	0.06	2.76
1.168	1.16	0.12	0.03	1.66	0.18	0.04	2.82
1.338	1.09	0.13	0.03	1.54	0.19	0.04	2.64
1.483	0.98	0.07	0.02	1.42	0.13	0.03	2.40
1.867	1.06	0.11	0.03	1.34	0.18	0.04	2.40
2.063	1.13	0.17	0.04	1.23	0.13	0.03	2.35
2.197	1.02	0.20	0.04	1.22	0.13	0.03	2.24
2.690	1.10	0.09	0.05	1.27	0.26	0.10	2.37
2.818	0.80	0.08	0.02	0.84	0.08	0.02	1.64

Table 3-9. Data obtained for breath duration components and tidal volume during progressive exercise in subject ZS.

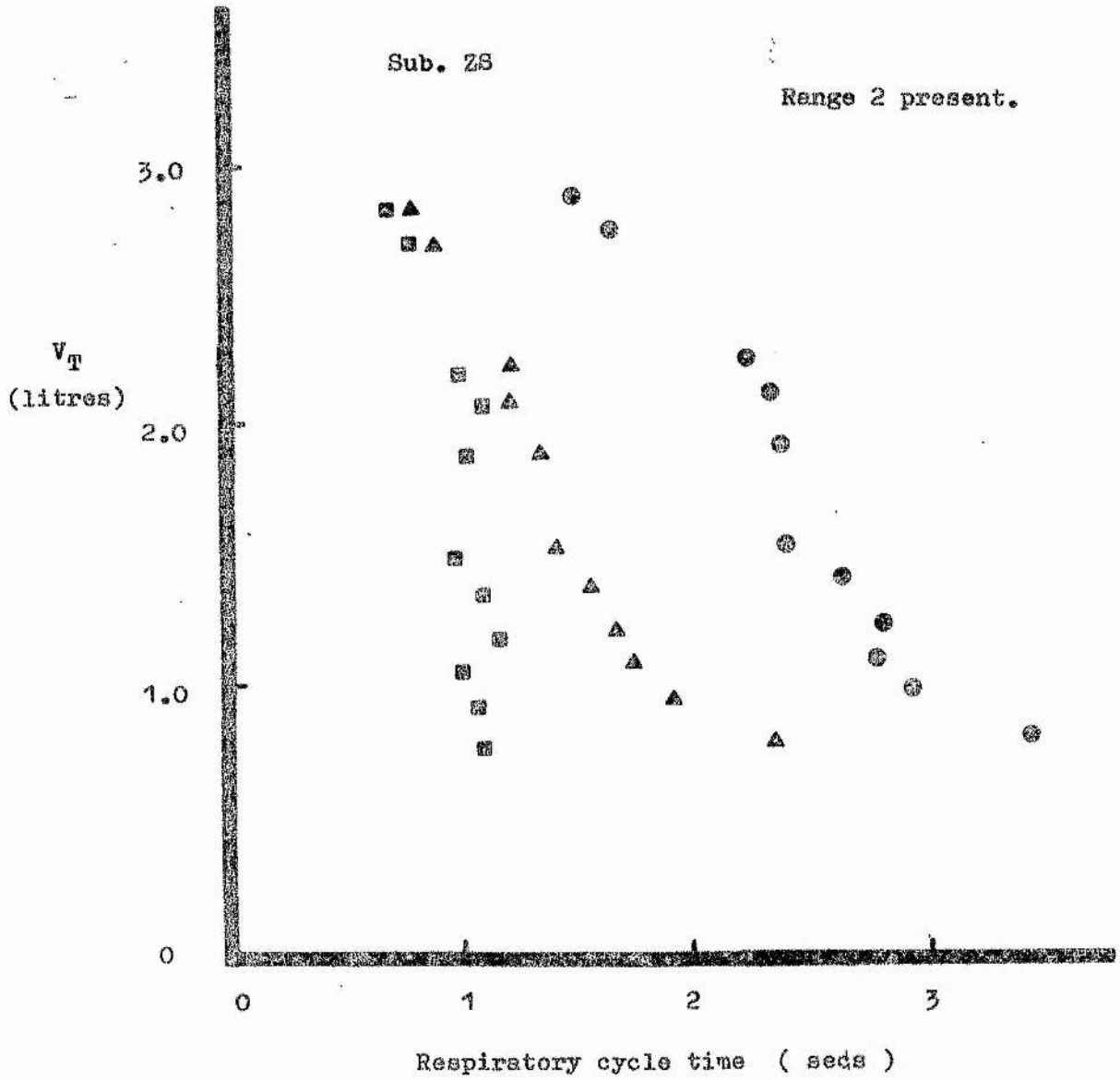


Fig. 3-9.

Tidal volume V_T plotted against respiratory cycle time during progressive exercise in one subject.

- ■ inspiratory time.
- ▲ expiratory time.
- ● total breath duration.

3-4 and 3-5). Only one subject (subject 3-3) showed both range 1 and 2. In range 2, after tidal volume exceeded twice resting level, $T_{insp.}$ shortened with tidal volume increases. (Fig. 3-6, Table 3-6).

c) Progressive exercise.

In all the 10 subjects studied, a similar pattern to progressive hypercapnia was shown. The total breath duration significantly shortened with increasing tidal volume, resulting from the significant shortening of expiratory time. The inspiratory time was constant in nine of the subjects studied at all levels of exercise with increasing tidal volume. A range 1 and 2 was found in one of the 10 subjects studied (Fig.3-9). The breaking point at which range 2 occurred was at 3 times the eupnoeic tidal volume value. (Figs. 3-7, 3-8 and 3-9, Tables 3-7, 3-8 and 3-9).

DISCUSSION

Clark and Euler 1972 from experiments during CO_2 rebreathing in cats and man, suggested that tidal volume is determined by the relationship between the mean flow rate (which is set by the respiratory drive) and the duration of inspiration. According to this proposed model, the inspiratory duration is set by central mechanism (range 1) until tidal volume exceeds a threshold value, above which increasing vagal activity leads to progressive shortening of inspiratory duration (range 2). They found that during CO_2 rebreathing in man there was a range 1 present where inspiratory duration was constant with increases in tidal volume up to 2 times eupnoeic values. The range 2, where inspiratory duration was volume dependent, was clearly present in the subjects studied.

This study has shown that in all the 3 types of ventilatory stimulation (hypercapnia, hypoxia and exercise), there was a significant decrease in total breath duration with increasing stimulation. With increasing tidal volume, there was a significant decrease in expiratory duration which was the main cause for the decreased $T_{tot.}$. The inspiratory time was constant at all levels of tidal volume in all except one subject during CO_2 rebreathing. In this subject a range 2 of Clark and Euler 1972 was observed in addition to range 1. Similar observations were found in the hypoxic and exercise studies where all except one subject showed con-

stant $T_{insp.}$ at all levels of tidal volume. Thus one subject in the hypoxic study and one in the exercise study showed both range 1 and range 2.

The findings here are in accordance with those of Cunningham and Gardner 1972. They analysed the breathing pattern of their subjects and found that with increasing PCO_2, $T_{tot.}$, shortened with increasing VT but $T_{insp.}$ was constant throughout the range studied. This showed that expiratory time shortened with increasing chemical load. Similarly, Jennett et al., 1974 found that in hypercapnia, $T_{insp.}$ was constant but $T_{exp.}$ and $T_{tot.}$ decreased with increasing VT. Davis and Stagg 1974 too found similar results in their steady state hypercapnic studies. Rebuck et al., 1976 found similar results in progressive hypercapnia.

The findings of constant $T_{insp.}$ with increasing VT in progressive hypoxia is similar to that of the steady state hypoxia studies of Jennett et al., 1974. In a similar study (progressive hypoxia), Rebuck et al., 1976 found that whilst range 1 was found in progressive hypercapnia, $T_{insp.}$ progressively shortened with increase in VT (or absence of range 1) in hypoxia.

In progressive exercise, a similar range 1 was found in that $T_{insp.}$ was constant up to level 4 times eupnoeic value of VT. After this point $T_{insp.}$ shortens. This is in accord with progressive exercise studies of Jennett et al., 1974.

Tidal volume and total breath duration are positively correlated from breath to breath in man (Priban 1963, Dejours et al., 1966, Cunningham et al., 1973). Also Kay et al., 1975 found similar results in steady-state exercise. In conscious humans, Barcroft and Margaria 1932 found that with increase in CO_2, the inspiratory flow rate increased linearly, in spite of variation in tidal volume and breath frequency. Davis and Stagg 1974 also found that in normal air-breathing, a VT against $T_{insp.}$ scatter plot showed tidal volume to be positively correlated with inspiratory time. Although the tidal volume and inspiratory time varied widely in their steady-state experiments, the relationship showed a linear relationship and their ratio remained relatively constant. Thus increases in minute volume were directly associated with increases in rate of rise of inspiratory activity at any level of ventilation. Also when the slope of VT with $T_{insp.}$ was compared at rest and raised CO_2 breathing, it showed a steeper slope during CO_2 breathing. This suggested that with increased respiratory stimulation, the slope or the mean inspiratory flow rate increased.

By taking $(dp/dt)_{max.}$ which measures the maximum rate of isometric contraction at about 0.1 second the subject-to-subject or breath-to-breath variation in pressure change occurring at later part of inspiration is eliminated. This change occurring at the later part of inspiration, reflects the influence of the timing

element of the respiratory centre. Whitlaw et al., 1975 has shown that the first 100 or 200 ms of an occluded breath of a conscious subject was quite reproducible. They also suggested that this probably represents the respiratory centre output of the respiratory centres in the interval before the obstruction is felt.

Although in this series of experiments, there were no investigations done on the VT and $T_{insp.}$ relationship during normal breathing, data from Davis and Stagg 1974 could still be applied. Since $T_{insp.}$ was held constant with increasing respiratory load thus increasing VT, as found in this study as well as those quoted above, and VT increases with $T_{insp.}$ at constant respiratory load (in Davis and Stagg 1974 scatter plot), it can be suggested that the mean inspiratory flow rate increases with increasing load. Since inspiratory flow rate reflects on the inspiratory pressure change, it can also be postulated from this that $(dp/dt)_{max.}$ which measures the maximum rate of isometric pressure change would show this change in the measurement of ventilatory drive.

CONCLUSION.

CONCLUSION.

This study was carried out to assess the reliability of $(dp/dt)_{max.}$ as an index of respiratory centre output. In Section 1A, it has been shown that whilst ventilation was reliable as an index of response to CO_2 in normal subjects, with added airways resistance there was a significant reduction in the CO_2 ventilation response slope. This makes it unreliable as a CO_2 response measurement in patients with airways obstruction. $(dp/dt)_{max.}$ was, however, not affected by the added airways resistance in normal subjects and thus was reliable as a CO_2 response measurement in patients with airways obstruction. The $P_{0.1}$ response to CO_2 showed that it was as good as $(dp/dt)_{max.}$ response as an index of CO_2 response. However, $(dp/dt)_{max.}$ has the advantage over $P_{0.1}$ that subjects do not sense the momentary occlusion and thus do not anticipate the next one. When the $(dp/dt)_{max.}$ and ventilatory response to isocapnic hypoxia was tested, it was shown that both give similar results. This would further suggest that $(dp/dt)_{max.}$ may be an index of the respiratory centre output.

To test further the reliability of $(dp/dt)_{max.}$, direct comparisons were made in anaesthetised rabbits (Section 1B). Thus it was shown that whilst ventilatory response to CO_2 was significantly reduced by added airways resistance, $(dp/dt)_{max.}$ response was not. Diaphragmatic electrical activity response to CO_2 too was unaltered by added airways resistance. Moreover $(dp/dt)_{max.}$ changes paralleled EMG changes with increasing PCO_2. This

suggests that $(dp/dt)_{max.}$ reflects respiratory neuron activity and can be said to be an index of muscle force generation and respiratory centre output.

Applications of $(dp/dt)_{max.}$ in normal subjects to test some recent findings showed that it is comparable to ventilation as an index of CO_2 responsiveness (Section 2). The findings that ventilatory response to exercise is positively correlated with ventilatory response to CO_2 has been confirmed here in a larger sample. The ventilatory exercise response too showed a positive correlation with $(dp/dt)_{max.}$ response to CO_2. Similarly it was found that trained subjects showed a higher $\dot{V}O_2$ max. and a lower CO_2 ventilatory response when compared with untrained. Amongst the untrained, when $\dot{V}O_2$ max. was taken as an index of fitness, it is shown that those who are physically fitter showed a lower response to hypercapnia and hypoxia when measured both in terms of ventilation and $(dp/dt)_{max.}$ response.

Studies on the breathing pattern (Section 3) during hypercapnia, hypoxia and exercise suggest that $(dp/dt)_{max.}$ changes may reflect on the increase in the mean inspiratory flow rate with increasing respiratory load.

Thus this study has shown that $(dp/dt)_{max.}$ is a reliable index of respiratory centre output, even in the face of mechanical obstruction.

BIBLIOGRAPHY.

REFERENCES

ALEXANDER, J. K., WEST, J. R., WOOD, J. A. and RICHARDS, D.W. (1955) Analysis of respiratory response to CO_2 inhalation in varying clinical states of hypercapnia, anoxia and acid base derangement. J. clin. Invest. 34: 511.

ALLEN, C., BENADE, M., DAVIES, C.T.M., DI PRAMPERO, P.E., HEDMAN, R., MERRIMAN, J., MYHRE, K., SHEPARD, R.J. and SIMMONS, R. (1968) Physiological responses to step, bicycle ergometer and treadmill exercise. J. Physiol. 198: 131P.

ALTOSE, M.D., KELSEN, S., STANLEY, N. and CHERNIACK, N. (1973) Isometric inspiratory contraction force and electromyographic activity of the diaphragm as measures of CO_2 sensitivity in man. J. clin. Invest. 52:39.

ALTOSE, M.D., STANLEY, N.N., CHERNIACK, N.S. and FISHMAN, A.P. (1975) Effects of mechanical loading and hypercapnia on inspiratory muscle EMG. J. appl. Physiol. 38:467.

ALTOSE, M.D., KELSEN, S.G., STANLEY, N.N., LEVINSON, R.S., CHERNIACK, N.S. and FISHMAN, A.P. (1976a) Effects of hypercapnia on mouth pressure during airway occlusion in conscious man. J. appl. Physiol. 40:338.

ALTOSE, M.D., KELSEN, S.G., STANLEY, N.N., CHERNIACK, N.S. and FISHMAN, A.P. (1976b) Effects of hypercapnia and flow-resistive loading on tracheal pressure during airway occlusion. J. appl. Physiol. 40:345.

ANTHONISEN, N.R. (1976) Some steady-state effects of respiratory loads. Chest. July Suppl. 70:168.

ARKINSTALL, W.W., NIRMEL, K., KLISSOURAS, V. and MILIC-EMILI, J. (1974) Genetic differences in the ventilatory response to inhaled CO_2. J. appl. Physiol. 36:6.

ASMUSSEN, E. and NEILSEN, M. (1946) Studies on the regulation of respiration in heavy work. Acta. physiol. scand. 12:171.

ASMUSSEN, E. and NEILSEN, M. (1956) Physiological dead space and alveolar gas pressures at rest and during muscular exercise. Acta. physiol. scand. 38:1.

ASMUSSEN, E. and NEILSEN, M. (1957) Measurements of arterial pO_2 in light and heavy exercise. Acta. physiol. scand. 42: Suppl. 145.

ASMUSSEN, E. and NEILSEN, M. (1958) Pulmonary ventilation and effect of oxygen breathing in heavy exercise. Acta. physiol. scand. 43:365.

ASMUSSEN, E. and NEILSEN, M. (1960) Alveolo-arterial gas exchange at rest and during work at different O_2-tensions. Acta. physiol. scand. 50:153.

ASTRAND, I. (1960) Aerobic work capacity in men and women with special reference to age. Acta. physiol. scand. 49: Suppl. 169.

ASTRAND, P.O. and RYHMING, I. (1954) A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work. J. appl. Physiol. 7:218.

ASTRAND, P.O. and CHRISTENSEN, E.H. (1964)"Aerobic Work Capacity"in F. Dickens, E. Neil and W.F. Widdas (ed.) "Oxygen in the Animal Organism" p.295, Pergamon Press, New York.

ASTRAND, P.O. and RODAHL (1970)"Textbook of Work Physiology" McGraw-Hill, London.

AVERY, M.E., CHERNICK, V., DUTTON, R.E. and PERMUTT, S. (1963) Ventilatory response to inspired carbon dioxide in infants and adults. J. appl. Physiol. 18:895.

BANNISTER, R.G. and CUNNINGHAM, D.J.C. (1954) The effects on the respiration and performance during exercise of adding oxygen to the inspired air. J. Physiol. 125:118.

BANNISTER, R.G., CUNNINGHAM, D.J.C. and DOUGLAS, C.G. (1954) The carbon dioxide stimulus to breathing in severe exercise. J. Physiol. 125:90.

BARCROFT, J. and MARGARIA, R. (1932) Some effects of carbonic acid in high concentration on respiration. J. Physiol. 74:156.

BARLTROP, D. (1954) The relation between body temperature and respiration. J. Physiol. 125:19P.

BARR, P.O., BECKMAN, M., BJURSTEDT, H., BRISMAR, J., HESSER and MATELL, G. (1964) Time courses of blood gas changes provoked by light and moderate exercise in man. Acta. physiol. scand. 60:1.

BERAL, V. and READ, D.J.C. (1971) Insensitivity of the respiratory centre to carbon dioxide in Enga people of New Guinea. Lancet 2:1290.

BISCOE, T.J. and PURVES, M.J. (1967) Factors affecting the cat carotid chemoreceptor and cervical sympathetic activity with special reference to passive hind-limb movements. J. Physiol. 190:425.

BISCOE, T.J., SAMPSON, S.R. and PURVES, M.J. (1967) Stimulus response curves of single carotid chemoreceptor afferent fibres. Nature 205:654.

BOYD, W.H. and BASMAJIAN, J.V. (1963) Electromyography of the diaphragm in rabbits. Am. J. Physiol. 204:943.

BRIGGS, M. (1920) Physical exertion, fitness and breathing. J. Physiol., London. 54:292.

BRODOVSKY, D., MACDONELL, J.A. and CHERNIACK, R.M. (1960) The respiratory response to carbon dioxide in health and in emphysema. J. clin. Invest. 39:724.

BROWN, E.B., Jr., and CLANCY, R.L. (1965) In vivo and in vitro CO_2 blood buffer curves. J. appl. Physiol. 20: 885.

BYRNE-QUINN, E., WEIL, J.V., SODAL, I.E., FILLEY, G.F. and GROVER, R.F. (1971) Ventilatory control in the athlete. J. appl. Physiol. 30:91.

CHERNIACK, R.M. and SNIDAL, D.P. (1956) The effect of obstruction to breathing on the ventilatory response to CO_2. J. clin. Invest. 35:1286.

CHERNIACK, N.S., LEDERER, D.H., ALTOSE, M.D. and KELSEN, S.G.(1976) "Occlusion pressure as a technique in evaluating respiratory control". Chest. July Suppl. 70:137.

CHIODI, H. (1957) Respiration adaptions to chronic high altitude hypoxia. J. appl. Physiol. 10:81.

CLARK, T.J.H. (1968) The ventilatory response to CO_2 in chronic airways obstruction measured by a rebreathing method. Clin. Sci. 34:559.

CLARK, T.J.H. and READ, D.J.C. (1966) A rebreathing method for studying the ventilatory response to CO_2. J. Physiol. 184:41P.

CLARK, T.J.H. and GODFREY, S. (1969) The effect of CO_2 on ventilation and breath-holding during exercise and while breathing through an added resistance. J. Physiol. 201:551.

CLARK, F.J. and VON EULER, C. (1972) On the regulation of depth and rate of breathing. J. Physiol. 222:267.

COHEN, J.J., BRACKETT, N.C. and SCHWARTZ, W.B. (1964) The nature of the carbon dioxide titration curve in the normal dog. J. clin. Invest. 43:777.

COHN, J.E., CARROLL, D.G. and RILEY, R.L. (1954) Respiratory acidosis in patients with emphysema. Am. J. Med. 17:447.

COMROE, J.H., Jr., (1944) The hyperpnea in muscular exercise. Physiol. Rev. 24:319.

COMROE, J.H. (1965) "Physiology of Respiration". Chicago Yearbook Pg. 192-198.

CORMACK, R.S., CUNNINGHAM, D.J.C. and GEE, J.B.L. (1957) The effect of carbon dioxide on the respiratory response to want of oxygen in man. Q. Jl. exp. Physiol. 42:303.

COTES, J.E. (1955) The role of body temperature in controlling ventilation during exercise in one normal subject breathing oxygen. J. Physiol. 129:554.

COTES, J.E., ALLSOPP, D. and SARDI, F. (1969) Human cardio-pulmonary responses to exercise: comparisons between progressive and steady-state exercise, between arm and leg exercise, and between subjects differing in body weight. Q. Jl. exp. Physiol. 54:211.

CROSS, K.W., HOOPER, J.M.D. and OPPE, T. (1953) The effect of inhalation of carbon dioxide on the respiration of the full term and premature infant. J. Physiol. 122:264.

CUMMING, R.G. (1967) Current levels of fitness. Canad. Med. Ass. J. 96:868.

CUNNINGHAM, D.J.C. (1963) Some quantitative aspects of the regulation of human respiration in exercise. Brit. Med. Bull. 19:25.

CUNNINGHAM, D.J.C. (1974) Integrative aspects of the regulation of breathing. In: MTP International Review of Science, Respiratory Physiology, edited by A.C. Guyton and J.G. Widdicombe. Butterworth. Series 1 Vol.2 pp.303-369.

CUNNINGHAM, D.J.C. and O'RIORDAN, J.L.H. (1957) The effect of a rise in the temperature of the body on the respiratory response to carbon dioxide at rest. Q. Jl. exp. Physiol. 42:329.

CUNNINGHAM, D.J.C., LLOYD, B.B. and PATRICK, J.M. (1963a) The relation between ventilation and end-tidal PCO_2 in man during moderate exercise with and without CO_2 inhalation. J. Physiol. 169:104P.

CUNNINGHAM, D.J.C., HAY, E.N., PATRICK, J.M. and LLOYD, B.B. (1963b) The effect of noradrenaline infusion on the relation between pulmonary ventilation and alveolar PO_2 and PCO_2 in man. Ann. N.Y. Acad. Sci. 109:756.

CUNNINGHAM, D.J.C., SPURR, D. and LLOYD, B.B. (1968). "The drive to ventilation from arterial chemoreceptors in hypoxic exercise". In: Arterial chemoreceptors ed. R.W. TORRANCE, Oxford. Blackwell. p.301.

CUNNINGHAM, D.J.C. and GARDNER, W.N. (1972) The relation between tidal volume and inspiratory and expiratory times during steady-state CO_2 inhalation in man. J. Physiol. 227:50P.

CUNNINGHAM, D.J.C., PEARSON, S.B. and GARDNER, W.N. (1973) Regulation of respiratory frequency and tidal volume at various ventilations. Archo. Fisiol. 69 Suppl. 433-446.

DAVIES, H., GAZETOPOULOS, N. and OLIVER, C. (1965) Ventilatory and metabolic response to graduated and prolonged exercise in normal subjects. Clin. Sci. 29:443.

DAVIES, C.T.M., GODFREY, S., LIGHT, M., SARGEANT, A.J. and ZEIDIFARD, E. (1975) Cardiopulmonary responses to exercise in obese girls and young women. J. appl. Physiol. 38:373.

DAVIS, NEWSOM, J. and STACG, D. (1975) Interrelationships of the volume and time components of individual breaths in resting man. J. Physiol. 245:481.

DEJOURS, P. (1959) La regulation de la ventilation au cours de l'exercise musculaire chez l'homme. J. Physiol. (Paris) 51:163.

DEJOURS, P. (1964) Control of respiration in muscular exercise. Handbook of Physiology. Section 3. Respiration Vol.1 (Ed. by W.O. Fenn and H. Rahn) American Physiological Society, Washington, D.C. pg.631-648.

DEJOURS, P., PUCCINELLI, R., ARMAND, J. and DICHARRY, M. (1966) Breath-to-breath variations of pulmonary gas exchange in resting man. Resp. Physiol. 1:265.

DERENNE, J.-Ph., COUTURE, J., ISCOE, S., WHITELAW, W.A. and MILIC-EMILI, J. (1976) Occlusion pressures in men rebreathing CO_2 under methoxyflurane anaesthesia. J. appl. Physiol. 40:805.

DOMIZI, D.B., PERKINS, J.F. and BYRNE, J.S. (1959) Ventilatory response to fixed acid evaluated by 'iso-PCO_2' technique. J. appl. Physiol. 14:557.

DRIPPS, D. and COMROE, J.H. Jr., (1947) The effect of the inhalation of high and low oxygen concentrations on respiration, pulse rate, ballistocardiogram and arterial oxygen saturation (oximeter) of normal individuals. Am. J. Physiol. 149:277

ECKENHOFF, J.E., HELRICH, M. and HEGE, M.J.D. (1956) A method for studying respiratory functions in awake or anaesthetised patients. Anesthesiology 17:66.

EDSTROM, H., CHOSLOVSKY, S. and CHERNIACK, R.M. (1976) The effect of lung volume on the ventilatory response to CO_2 during resistive loading in normal subjects. Am. Rev. Resp. Dis. 114:761.

EKBLOM, B. and GJESSING, E. (1968) Maximal oxygen uptake of the Easter Island population. J. appl. Physiol. 25:124.

ELDRIDGE, F.L. (1971) Relationship between phrenic nerve activity and ventilation. Am. J. Physiol. 221:535.

ELDRIDGE, F.L. (1975) Relationship between respiratory nerve and muscle activity and muscle force output. J. appl. Physiol. 39:567.

ELDRIDGE, F. and DAVIS, J.M. (1959) Effect of mechanical factors on respiratory work and ventilatory responses to CO_2. J. appl. Physiol. 14:721.

ENGHOFF, H. (1938) Volumen inefficax. Upsala Lakar Foren, Forh. 44:191.

VON EULER, C., HERRERO, F. and WEXLER, I. (1970) Control mechanisms determining rate and depth of respiratory movements. Resp. Physiol. 10:93.

EVANICH, M.J., FRANCO, M.J. and LOURENCO, R.V. (1973) Force output of the diaphragm as a function of phrenic nerve firing rate and lung volume. J. appl. Physiol. 35:208.

EVANICH, M.J. and LOURENCO, R.V. (1974) Relationships between phrenic motor nerve activity and intratracheal and intrapleural pressures. Fed. Proc. (Abstract) 33:1180.

EVANICH, M.J. and LOURENCO, R.V. (1976) Frequency response analysis of the diaphragm in vivo. J. appl. Physiol. 40:726.

EVANICH, M.J., LOPATA, M. and LOURENCO, R.V. (1976) Phrenic nerve activity and occlusion pressure changes during CO_2 rebreathing in cats. J. appl. Physiol. 41:536.

FAGRAEUS, L., HESSER, C.M. and LINNARSSON, D. (1974) Cardiorespiratory responses to graded exercise at increased ambient air pressure. Acta. physiol. scand. 91:259.

FAULKNER, J.A., ROBERTS, D.E., ELK, R.L. and CONWAY, J. (1971) Cardiovascular responses to submaximum and maximum effort cycling and running. J. appl. Physiol. 30:457.

FENCL, V., MILLER, T.B. and PAPPENHEIMER, J.R. (1966) Studies on respiratory response to disturbances of acid-base balance, with deductions concerning ionic composition of cerebral interstitial fluid. Am. J. Physiol. 210:459.

FILLEY, G.F., GREGOIRE, F. and WRIGHT, F.W. (1954) Alveolar and arterial oxygen tensions and the significance of the alveolar-arterial oxygen tension difference in normal man. J. clin. Invest. 33:517.

FISHMAN, A.P., SAMET, P. and COURNAND, A. (1955) Ventilatory drive in chronic pulmonary emphysema. Am. J. Med. 19:533.

FITZGERALD, R.S., GARFINKEL, F., SILBERGELD, E. and LOSCUTOFF, S.C. (1976) Factors in the interpretation of mouth occlusion pressure during measurements of chemosensitivity. Chest. July Suppl. 70:145.

FLENLEY, D.C., PENGELLY, L.D. and MILIC-EMILI, J. (1971) Immediate effects of positive-pressure breathing on the ventilatory response to CO_2. J. appl. Physiol. 30:7.

FOWLE, A.S.E. and CAMPBELL, E.J.M. (1961) The immediate carbon dioxide storage capacity in man. Clin. Sci. 27:41.

FRITTS, H.W., FISHMAN, A.P. and COURNAND, A. (1957) Factors contributing to the diminished ventilatory response to CO_2 of patients with obstructive emphysema. Fed.Proc.16:41.

FRITTS, H.W., FILLER, J., FISHMAN, A.P. and COURNAND, A. (1959) The efficiency of ventilation during voluntary hyperpnea studies in normal subjects and in dyspneic patients with either chronic pulmonary emphysema or obesity. J. clin. Invest. 38:1339.

GALDSTON, M. and WOLLACK, A.C. (1947) Oxygen and carbon dioxide tensions of alveolar air and arterial blood in healthy young adults at rest and after exercise. Am. J. Physiol. 151:276.

GEMMILL, C.L. and REEVES, D.L. (1933) Effect of anoxemia in normal dogs before and after denervation of carotid chemoreceptors. Am. J. Physiol. 105:487.

GODFREY, S., EDWARDS, R.H.T., COPLAND, G.M. and GROSS, P.L. (1971) Chemosensitivity in normal subjects, athletes, and patients with chronic airways obstruction. J. appl. Physiol. 30:193.

GOLDRING, R.M. and TURINO, G.M. (1976) Assessment of respiratory regulation in chronic hypercapnia. Chest July Suppl. 70:186.

GRASSINO, A.E., LEWINSOHN, G.E. and TYLER, J.M. (1973) Effects of hyperinflation of the thorax on the mechanics of breathing. J. appl. Physiol. 35:336.

GRAY, J.S. (1946) The multiple factor theory of the control of respiratory ventilation. Science 103:739.

GRAY, B.A. (1968) Response of the perfused carotid body to changes in pH and PCO_2. Resp. Physiol. 4:229.

GRODINS, F.S. (1950) Analysis of factors concerned in regulation of exercise. Physiol. Rev. 30:220.

GRUNSTEIN, M.M., YOUNES, M. and MILIC-EMILI, J. (1973) Control of tidal volume and respiratory frequency in anaesthetised cats. J. appl. Physiol. 35:463.

GUZ, A., NOBLE, M.I.M., WIDDICOMBE, J.G., TRENCHARD, D. and MUSHIN, W.W. (1966) The effect of bilateral block of vagus and glossopharyngeal nerves on the ventilatory response to CO_2 in conscious man. Resp. Physiol. 1:206.

HEISTAD, D.D., WHEELER, R.C., MARK, A.L., SCHMID, P.G. and ABBOUD, F.M. (1972) Effects of adrenergic stimulation on ventilation in man. J. clin. Invest. 51:1469.

HENRY, J.G. and BAINTON, C.R. (1974) Human core temperature increase as a stimulus to breathing during moderate exercise. Resp. Physiol. 21:183.

HERMANSEN, L. (1971) Lactate production during exercise. Advances in Experimental Medicine and Biology. Vol.2. Proceedings of the Karolinska Institutet Symposium held in Stockholm, Sweden. Sept. 6-9th, 1970.

HERMANSEN, L. (1973) Oxygen transport during exercise in human subjects. Acta. physiol. scand. Suppl. 399.

HERMANSEN, L. and OSEID, S. (1971) unpublished. Quoted in HERMANSEN, L. (1973) Oxygen transport during exercise in human subjects. Acta. physiol. scand. Suppl.399.

HEY, E.N., LLOYD, B.B., CUNNINGHAM, D.J.C., JUKES, M.G.M. and BOLTON, D.P.G. (1966) Effects of various respiratory stimuli on the depth and frequency of breathing in man. Resp. Physiol. 1:193.

HICKMAN, J.B., PRYOR, W.W., PAGE, E.B. and ATWELL, R.J. (1951) Respiratory regulation during exercise in unconditioned subjects. J. clin. Invest. 30:503.

HIRSHMAN, C.A., McCULLOUGH, R.E. and WEIL, J.V. (1975) Normal values for hypoxic and hypercapnic ventilatory drives in man. J. appl. Physiol. 38:1095.

HOLMGREN, A. and LINDERHOLM, H. (1958) Oxygen and carbon dioxide tensions of arterial blood during heavy and exhaustive exercise. Acta. physiol. scand. 44:203.

HOLMGREN, A. and McILROY, M.B. (1964) Effect of temperature on arterial blood gas tensions and pH during exercise. J. appl. Physiol. 19: 243.

HOLTON, P. and WOOD, J.B. (1965) The effects of bilateral removal of the carotid bodies and denervation of the carotid sinuses in two human subjects. J. Physiol. 181:365.

HORNBEIN, T.F. and ROOS, A. (1963) Specificity of H ion concentration as a carotid chemoreceptor stimulus. J. Appl. Physiol. 18:580.

HUGHES, R.L., CLODE, M., EDWARDS, R.H.T. et al (1968) Effect of inspired O_2 on cardiopulmonary and metabolic responses to exercise in man. J. appl. Physiol. 24:336.

HURTADO, A. (1960) Some chemical aspects of life at high altitudes. Ann. Internal Med. 53:247.

IKAI, M. and KITAGAWA (1972) Maximum oxygen uptake of Japanese related to sex and age. Med. and Sci. in Sports 4:127.

ISAZA, G.D., POSNER, J.D., ALTOSE, M.D., KELSEN, S.G. and CHERNIACK, N.S. (1975) The effect of inspiratory flow resistance and anaesthesia on the isometric inspiratory muscle force during hypercapnia. Fed. Proc. (Abstract) 34:786.

ISCOE, S., DANKOFF, J., MIGICOVSKY, R. and POLOSA, C. (1976) Recruitment and discharge frequency of phrenic motorneurones during respiration. Resp. Physiol. 26:113.

JENNETT, S. (1968) Assessment of respiratory effects of analgesic drugs. Brit. J. Anaesth. 40:746.

JENNETT, S. (1969a) Changes in ventilation and heart rate during and after brief moderate hyoxia in resting man. J. Physiol. 200:106P.

JENNETT, S. (1969b) Hypoxia and hyperoxia in man. Ph.D. Thesis, University of Glasgow.

JENNETT, S. and SHORT, H.H. (1973) Assessment of respiratory chemosensitivity by a rebreathing method. B.J. Anaesth. 45:119.

JENNETT, S., RUSSEL, T. and WARNOCK, K.A. (1974) The duration of inspiration during changing states of ventilation in man. J. Physiol. 238:54P.

JONES, N.L., McHARDY, G.J.R., NAIMARK, A., et al., (1966) Physiological dead space and alveolar-arterial gas pressure differences during exercise. Clin. Sci. 31:19.

KARLSON, J., DIAMANT, B. and SALTIN, B. (1971) Muscle metabolites during submaximal and maximal exercise in man. Scan-J. Clin. Lab. Invest. 21:1.

KATSAROS, G., LOESCHCKE, H.H., LERCHE, D., SCHONTHAL, H. and HAHN, N. (1960) Wirkung der bikarbonat-alkalose auf die lungenbeluftung beim menschen. Bestimmung der teilwirkungen von pH und CO_2-druck auf die ventilation und vergleich mit dem ergebnissen bie acidose. Pflugers Arch. ges. Physiol. 271: 732.

KAY, J.D.S., PETERSEN, E.S. and VEJBY-CHRISTENSEN, H. (1975) Mean and breath-by-breath pattern of breathing in man during steady-state exercise. J. Physiol. 251:657.

KEARNEY, J.T., STULL, G.A., EWING, J.L. and STREIN, J.W. (1976) Cardiorespiratory responses of sedentary college women as a function of training intensity. J.appl. Physiol. 41:822.

KELSEN, S.G., ALTOSE, M.D., STANLEY, N.N., LEVINSON, R.S., CHERNIACK, N.S. and FISHMAN, A.P. (1976) Effect of hypoxia on the pressure developed by inspiratory muscles during airway occlusion. J. appl. Physiol. 40:372.

KELTZ, H., SAMORTIN, T. and STONE, D.J. (1972) Hyperventilation: a manifestation of exogenous beta-adrenergic stimulation. Am. Rev. Resp. Dis. 105:637.

KOZLOWSKI, S., RASMUSSEN, B. and WILKOFF, W.G. (1971) The effect of high oxygen tension on ventilation during severe exercise. Acta. physiol. scand. 81:385.

KRYGER, M.H., YACOUB, O. and ANTHONISEN, N.R. (1975) Effect of inspiratory resistance on occlusion pressure in hypoxia and hypercapnia. Resp. Physiol. 24:241.

LALLY, D.A., ZECHMAN, F.W. and TRACY, R.A. (1974) Ventilatory responses to exercise in divers and non-divers. Resp. Physiol. 20: 117.

LAMBERTSEN, C.J. (1960) Carbon dioxide and respiration in acid-base homeostasis. Anaesthesiology. 21:642.

LAMBERTSEN, C.J., OWEN, S.G., WENDEL, HERBERT, STROUD, MORRIS, W., LURIE, ABRAHAM, A., LOCHNER, WILHELM and CLARK, GORDON, F. (1959) Respiratory and cerebral circulatory control during exercise at .21 and 2.0 atmospheres inspired PO_2. J. appl. Physiol. 14:966.

Lambertsen, C.J., SEMPLE, S.J.G., SMYTH, M.G. and GELFAND. (1961) H^+ and PCO_2 as chemical factors in respiratory and cerebral circulatory control. J. appl. Physiol. 16:473.

LANE, D.J. and HOWELL, J.B.L. (1970) Relationship between sensitivity to carbon dioxide and clinical features in patients with chronic airways obstruction. Thorax. 25:150.

LEITCH, A.G., CLANCY, L. and FLENLEY, D.C. (1975) Maximal oxygen uptake, lung volume and ventilatory response to carbon dioxide and hypoxia in a pair of identical twin athletes. Clin. Sci. Molec. Med. 48:235.

LEUSEN, I. (1954) Chemosensitivity of the respiratory center: Influence of changes in the H^+ and total buffer concentration in the cerebral ventricle on respiration. Am. J. Physiol. 176:513.

LEUSEN, I. (1963) Aspects of the chemosensitivity of the respiratory centres in the regulation of human respiration. In: The Regulation of Human Respiration ed. D.J.C. Cunningham and B.B. Lloyd, F.A. Davis, Philadelphia. pg.207.

LEUSEN, I.R. and DEMEESTER, G. (1960) Die chemische reaktion der cerebrospinalflussigkeit im Sauerstoffmangel. Pflugers Arch. ges. Physiol. 270:390.

LILIENTHAL, J.L., RILEY, R.L., PROEMMEL, D.D. and FRANKE, R.E. (1946) An experimental analysis in man of the oxygen pressure gradient alveolar air to arterial blood during rest and exercise at sea level and at altitude. Am. J. Physiol. 147:199

LINDERHOLM, H. (1959) Diffusing capacity of the lungs as a limiting factor for physical working capacity. Acta. med. scand. 163:61.

LIPPOLD, O.C.J. (1952) The relation between integrated action potentials in a human muscle and its isometric tension. J. Physiol. 117:492.

LLOYD, B.B. (1963) The chemical stimulus to breathing. Brit. med. bull. 19:10.

LLOYD, B.B., JUKES, M.G.M. and CUNNINGHAM, D.J.C. (1958) The relation between alveolar oxygen pressure and the respiratory response to carbon dioxide in man. Q. Jl. exp. Physiol. 43:214.

LOESCHKE, H.H. and MITCHELL, R.A. (1963) Properties and localisation of intracranial chemosensitivity in the regulation of human respiration. In: The regulation of human respiration. Edited by D.J.C. Cunningham and B.B. Lloyd, F.A. Davis, Philadelphia. p243.

LOPATA, M., LA FATA, J., EVANICH, M.J. and LOURENCO, R.V.(1977) Effects of flow-resistive loading on mouth occlusion pressure during CO_2 rebreathing. Am. Rev. Resp. Dis. 115:73.

LOURENCO, R.V., TURINO, G.M., DAVIDSON, L.A.G. and FISHMAN, A.P. (1965) Regulation of ventilation in diffuse pulmonary fibrosis. Am. J. Med. 38:199.

LOURENCO, R.V., CHERNIACK, N.S., MALM, J.R. and FISHMAN, A.P. (1966) Nervous output from respiratory center during obstructed breathing. J. appl. Physiol. 21:527.

LOURENCO, R.V., and MIRANDA, J.M. (1968) Drive and performance of the ventilatory apparatus in chronic obstructive lung disease. N. Engl. J. Med. 279:53.

LUGLIANI, R., WHIPP, B.J., SEARD, C. and WASSERMAN, K. (1971) Effect of bilateral carotid body resection on ventilatory control at rest and during exercise in man. N. Engl. J. Med. 285:1105.

LYALL, J.R.W. and CAMERON, I.R. (1974) The relation between vital capacity and the respiratory response to inhaled carbon dioxide. Eur. Soc. Clin. Invest. (Abstract) 4:338.

LYNNE-DAVIES, P., COUTURE, J., PENGELLY, L.D. and MILIC-EMILI, J. (1971) Immediate ventilatory response to added inspiratory elastic loads in cats. J. appl. Physiol. 30:512.

MARANETRA, N. and PAIN, M.C.P. (1974) Ventilatory drive and ventilatory response during rebreathing. Thorax 29:578.

MARGARIA, R., AGHEMD, P. and ROVELL. (1965) Indirect determination of maximal O_2 consumption in man. J. appl. Physiol. 20:1070.

MARSHALL, R. (1962) Relationships between stimulus and work of breathing at different lung volumes. J. appl. Physiol. 17:917.

MATELL, G. (1963) Time courses of changes in ventilation and arterial gas tensions in man induced by moderate exercise. Acta. physiol. scand. 58: (Suppl.206).

MATTHEWS, A.W. and HOWELL, J.B.L. (1974) Assessment of CO_2 responsiveness by maximum rate of change of mouth pressure during initial transient respiratory obstruction. Clin. Sci. Molec. Med. 46:19P.

MATTHEWS, A.W. and HOWELL, J.B.L. (1975) The rate of isometric inspiratory pressure development as a measure of responsiveness to carbon dioxide in man. Clin. Sci. Molec. Med. 49:57.

MATTHEWS, A.W. and HOWELL, J.B.L. (1976) Assessment of responsiveness to carbon dioxide in patients with chronic airways obstruction by rate of isometric inspiratory pressure development. Clin. Sci. Molec. Med. 50:199.

MILIC-EMILI, J. and TYLER, J.M. (1963) Relation between work output of respiratory muscles and end-tidal CO_2 tension. J. appl. Physiol. 18:497.

MINH, V-D., DOLAN, G.F., KONOPKA, R.F. and MOSER, K.M. (1976) Effect of hyperinflation on inspiratory function of the diaphragm. J. appl. Physiol. 40:67.

MITCHELL, R.A. (1965) The regulation of respiration in metabolic acidosis and alkalosis. In: Cerebrospinal fluid and the regulation of ventilation. Ed. by C.Mc.C. BROOKS, F.F. KAO and B.B. LLOYD. Oxford, Blackwell Scientific. 105-131.

MITCHELL, J.H., SPROULE, B.J. and CHAPMAN, C.B. (1958) Physiological meaning of the maximal oxygen intake test. J. clin. Invest. 37:538.

MITCHELL, R.A., MASSION, W., CARMEN, C.T. and SEVERINGHAUS, J.W. (1960) Fourth ventricle respiratory chemosensitivity and urea postrema. Fed. Proc. 19:374.

MITCHELL, R.A., LOESCHEKE, H.H., MASSION, W. and SEVERINGHAUS, J.W. (1963) Respiratory response mediated through superficial chemosensitive areas on the medulla. J. appl. Physiol. 18:523.

MITCHELL, R.A. and SINGER, M.M. (1965) Respiration and cerebrospinal fluid pH in metabolic acidosis and alkalosis. J. appl. Physiol. 20:905.

NEILSEN, M. (1936) Untersuchungen uber die atemregulation beim menschen, besonders mit hinblick auf die art des chemischen reizes. Skand. Arch. Physiol. 74: Suppl.10.

NEILSEN, M. and SMITH, H. (1952) Studies on the regulation of respiration in acute hypoxia with an appendix on respiratory control during prolonged hypoxia. Acta. physiol. scand. 24:293.

NORTH, J.B. and JENNETT, S. (1976) Response of ventilation and of intracranial pressure during rebreathing of carbon dioxide in patients with acute brain damage. Brain. 99:169.

O'DONNELL, T.V. and HOOD, L.J. (1971) Decreased chemoreceptor sensitivity and chronic obstructive lung disease. J. Roy. Coll. Phycns. London. 6:53.

PAPPENHEIMER, J.R., FENCL, V., HEISEY, S.R. and HELD. (1965) Role of cerebral fluids in control of respiration as studied in unanaesthetised goats. Am. J. Physiol. 208:436.

PARK, S.S. (1965) Factors responsible for carbon dioxide retention in chronic obstructive lung disease. Am. Rev. Resp. Dis. 92:245.

PATRICK, J.M. and HOWARD, A. (1972) The influence of age, sex, body size and lung size on the control and pattern of breathing during CO_2 inhalation in caucasians. Resp. Physiol. 16:337.

PENGELLY, L.D., GREENER, J., BOWMER, I., LUTERMAN, A. and MILIC-EMILI, J. (1975) Effect of added elastances on the first loaded breath in man. J. appl. Physiol. 38:39.

PETERSEN, E.S. and VEJBY-CHRISTENSEN, H. (1973). Effect of body temperature on steady state ventilation and metabolism in exercise. Acta. physiol. scand. 89:342.

PRIBAN, I.P. (1963) An analysis of some short-term patterns of breathing in man at rest. J. Physiol. 166: 425.

PRIME, F.J. and WESTLAKE, E.K. (1953) The respiratory response to CO_2 in emphysema. Clin. Sci. 13:321.

PUGH, L.G.C.E., GILL, M.B., LANIRI, S., MILLEDGE, J.S., WARD, M.D. and WEST, J.B. (1964) Muscular exercise at great altitudes. 19:431.

READ, D.J.C. (1967) A clinical method for assessing the ventilatory response to carbon dioxide. Australasian Ann. Med. 16:20.

READ, D.J.C. and LEIGH, J. (1967) Blood-brain tissue PCO_2 relationships and ventilation during rebreathing. J. appl. Physiol. 23:53.

REBUCK, A.S. and READ, D.J.C. (1971) Patterns of ventilatory response to CO_2 during recovery from severe asthma. Clin. Sci. 41:13.

REBUCK, A.S., JONES, N.L. and CAMPBELL, E.J.M. (1972) Ventilatory response to exercise and to CO_2 rebreathing in normal subjects. Clin. Sci. 43:861.

REBUCK, A.S., KANGALEE, M., PENGELLY, L.D. and CAMPBELL, E.J.M. (1973) Correlation of ventilatory responses to hypoxia and hypercapnia. J. appl. Physiol. 35:173.

REBUCK, A.S., RIGG, J.R.A., KANGALEE, M. and PENGELLY, L.D. (1974) Control of tidal volume during rebreathing. J. appl. Physiol. 37:475.

REBUCK, A.S., RIGG, J.R.A. and SAUNDERS, N.A. (1976) Respiratory frequency response to progressive isocapnic hypoxia. J. Physiol. 258:19.

RICHARDS, D.W., FRITTS, H.W. and DAVIS, A.L. (1958) Observations on the control of respiration in emphysema: The effects of oxygen on ventilatory response to CO_2 inhalation. Trans. Ass. Amer. Phycns. 71:142.

RICHARDSON, P.S. and WIDDICOMBE, J.G. (1965) Ventilatory responses to carbon dioxide in rabbits before and after cervical vagotomy. J. Physiol. 181:43P.

RICHARDSON, P.S. and WIDDICOMBE, J.G. (1969) The role of the vagus nerves in the ventilatory responses to hyperoapnia and hypoxia in anaesthetised and unanaesthetised rabbits. Resp. Physiol. 7:122.

RIGG, J.R.A., REBUCK, A.S. and CAMPBELL, E.J.M. (1974) Effect of posture on the ventilatory response to CO_2 J. appl. Physiol. 37:487.

RILEY, R.L. (1954) Work of breathing and its relation to respiratory acidosis. Ann. Int. Med. 41:172.

ROBINSON, S. (1963) Temperature regulation in exercise. Pediatrics 32:691.

SAITO, K., HONDA, Y. and HASAMURA, N. (1960) Evaluation of respiratory response to changes in PCO_2 and hydrogen ion concentration of arterial blood in rabbits and dogs. Jap. J. Physiol. 10:634.

SALTIN, B., BLOMQVIST, G., MITCHELL, J.H., JOHNSON, R.L., WILDENTHAL, K. and CHAPMAN, C.B. (1968) Response to exercise after bed rest and after training. Circulation. 38 (Suppl.7).

SANT'AMBROGIO, G. and SAIBENE, F. (1970) Contractile properties of the diaphragm in some mammals. Resp. Physiol. 10:349.

SAUNDERS, N.A., HEILPERN, S. and REBUCK, A.S. (1972) Relation between personality and ventilatory response to carbon dioxide in normal subjects: A role in asthma? Br. Med. J. 1:719.

SAUNDERS, N.A., LEEDER, S.R. and REBUCK, A.S. (1976) Ventilatory response to carbon dioxide in young athletes: a family study. Am. Rev. Resp. Dis. 113:497.

SCHAEFER, K.E. (1955) The role of carbon dioxide in the physiology of human diving. In: Proceedings of the underwater Physiology Symposium: ed. L.G. Goff, Washington, D.C. National Academy of Science. National Research Council. pg. 131-139.

SCHAEFER, K.E. (1965) Adaptation to breath-hold diving. In: Physiology of Breath-hold Diving and the Ama of Japan, edited by H. Rahn and T. Yokoyamu. Washington, D.C. National Research Council Publication. 1341: 237-252.

SCHAEFER, K.E. (1958) Respiratory pattern and respiratory response to CO_2. J. appl. Physiol. 13:1.

SCHAEFER, K.E., HASTINGS, B.J., CAREY, C.R. and NICHOLS, G. (1963) Respiratory acclimatisation to carbon dioxide. J. appl. Physiol. 18:1071.

SHAFER, K.E. (1949) Atmung und saure-basen gleichgewicht bei lang dauerndem aufenthalt in 3% CO_2. Pflueger Arch. Ges. Physiol. 251:689.

SCOTT, R.W. (1920) Observations on the pathologic physiology of chronic pulmonary emphysema. Arch. Intrnl. Med. 26:544.

SEVERINGHAUS, J.W., MITCHELL, R.A., RICHARDSON, B.W. and SINGER, M.M. (1963) Respiratory control at high altitude suggesting active transport regulation of csf pH. J. appl. Physiol. 18:1155.

SEVERINGHAUS, J.W., BAINTON, C.R. and CARCELEN, A. (1966) Respiratory insensitivity to hypoxia in chronically hypoxic man. Resp. Physiol. 1:308.

SHANNON, N. and ZECHMAN, F.W. (1972) The reflex and mechanical response of the inspiratory muscles to an increased airflow resistance. Resp. Physiol. 16:51.

SONG, S.H., KANG, D.H., KANG, B.S. and HONG, S.K. (1963) Lung volumes and ventilatory response to high CO_2 and low O_2 in the Ama. J. appl. Physiol. 18:466.

SORENSEN, S.C. (1971) The chemical control of ventilation. Acta. physiol. scand. Suppl. 361.

SORENSEN, S.C. and SEVERINGHAUS, J.W. (1968) Irreversible respiratory insensitivity to acute hypoxia in man born at high altitude. J. appl. Physiol. 25:217.

SORENSEN, S.C. and CRUZ, J.C. (1969) Ventilatory response to a single breath of CO_2 in O_2 in normal man at sea level and high altitude. J. appl. Physiol. 27:186.

SORENSEN, S.C. and MINES, A.H. (1970) Ventilatory responses to acute and chronic hypoxia in goats after sinus nerve section. J. appl. Physiol. 28:832.

SPIRO, S.G., JUNIPER, E., BOWMAN, P. and EDWARDS, R.H.T. (1974) An increasing work rate test for assessing the physiological strain of submaximal exercise. Clin. Sci. Molec. Med. 46:191.

SALTIN, B. and ASTRAND, P.O. (1967) Maximal O_2 uptake in athletes. J. appl. Physiol. 23:353.

STAMFORD, B.A. (1975) Maximal oxygen uptake during treadmill walking and running at various speeds. J. appl. Physiol. 39:386.

STANLEY, N.N. (1977) Evaluation of the occlusion pressure response to hypercapnia. Clin. Sci. 52:12P.

STANLEY, N.N., ALTOSE, M.D., CHERNIACK, N.S. and FISHMAN, A.P. (1975) Changes in strength of lung inflation reflex during prolonged inflation. J. appl. Physiol. 38:474.

STRACHOVA, Z. and PLUM, F. (1973) Reproducibility of the rebreathing carbon dioxide response test using an improved method. Am. Rev. Resp. Dis. 107:864.

STREMEL, R.W., CONVERTINO, V.A., BERNAUER, E.M. and GREENLEAF, J.E. (1976) Cardiorespiratory deconditioning with static and dynamic leg exercise during bed rest. J. appl. Physiol. 41:905.

SUSKIND, MITZI, BRUCE, R.A., McDOWELL, M.E., YU, P.N.G., and LOVEJOY, F.W. (1950) Normal variations in end-tidal air and arterial blood carbon dioxide and oxygen tensions during moderate exercise. J. appl. Physiol. 3:282.

TAYLOR, C. (1941) Studies in exercise physiology. Amer. J. Physiol. 135:27.

TAYLOR, H.L., HENSCHEL, A., BROZEK, J. and KEYS, A. (1949) Effects of bed rest on cardiovascular function and work performance. J. appl. Physiol. 2:223.

TAYLOR, H.L., BUSKIRK, E. and HENSCHEL, A. (1955) Maximum oxygen intake as an objective measure of cardio-respiratory performance. J. appl. Physiol. 8:73.

TENNEY, S.M., REMMERS, J.E. and MITHOEFER, J.C. (1963) Interaction of CO_2 and hypoxic stimuli on ventilation at high altitude. Q. Jl. exp. Physiol. 48:192.

TENNEY, S.M. and BROOKS, J.G. (1966) Carotid bodies, stimulus interaction and ventilatory control in unanaesthetised goats. Resp. Physiol. 1:211.

TURINO, G.M. and GOLDRING, R.M. (1976) Techniques for measuring the responsiveness of the ventilatory apparatus in man in disease. Chest. July Suppl. 70:180.

VANCE, J.W. (1966) Stores of carbon dioxide in emphysema. Dis. of Chest. 49:147.

VON DOBELN, W. and HOLMER, I. (1967) Body composition, sinking force and oxygen uptake of man treading water. J. appl. Physiol. 22:934.

WADE, J.G., LARSON, C.P., HICKEY, R.F., EHRENFELD, W.K. and SEVERINGHAUS, J.W. (1970) Effects of carotid endarterectomy on the carotid chemoreceptor and baroreceptor function in man. N. Engl. J. Med. 282:823.

WASSERMAN, K., VAN KESSEL, A.L. and BURTON, G.G. (1967) Interaction of physiological mechanisms during exercise. J. appl. Physiol. 22:71.

WASSERMAN, K., WHIPP, B.J., KOYAL, S.N. and BEAVER, W.L. (1973) Anaerobic threshold and respiratory gas exchange during exercise. J. appl. Physiol. 35:236.

WASSERMAN, K., WHIPP, B.J., KOYAL, S.N. and CLEARY, M.G. (1975) Effect of carotid body resection on ventilatory and acid-base control during exercise. J. appl. Physiol. 39:354.

WEIL, J.V., BYRNE-QUINN, E., SODAL, I.E., FRIESEN, W.O., UNDERHILL, B., FILLEY, G.F. and GROVER, R.F. (1970) Hypoxic ventilatory drive in normal man. J. clin. Invest. 49:1061.

WEIL, J.V., BYRNE-QUINN, E., SODAL, I.E., FILLEY, G.F. and GROVER, R.F. (1971) Acquired attenuation of chemoreceptor function in chronically hypoxic man at high altitude. J. clin. Invest. 50:186.

WEIL, J.V., BYRNE-QUINN, E., SODAL, I.E., KLINE, J.S., McCULLOUGH, R.E. and FILLEY, G.F. (1972) Augmentation of chemosensitivity during mild exercise in normal man. J. appl. Physiol. 33:813.

WHIPP, B.J. and WASSERMAN, K. (1969) Alveolar-arterial gas tension differences during graded exercise. J. appl. Physiol. 27:361.

WHIPP, B.J. and WASSERMAN, K. (1970) Effect of body temperature on the ventilatory response to exercise. Resp. Physiol. 8:354.

WHIPP, B.J. and WASSERMAN, K. (1972) Oxygen uptake kinetics for various intensities of constant load work. J. appl. Physiol. 33:351.

WHITELAW, W.A., DERENNE, J-Ph. and MILIC-EMILI, J. (1975) Occlusion pressure as a measure of respiratory center output in conscious man. Resp. Physiol. 23:181.

WILEY, R.L. and ZECHMAN, F.W. (1969) Transient respiratory responses to step changes in airflow resistance in anaesthetised cats. Resp. Physiol. 6:105.

WOLDRING, S. (1965) Interrelationships between lung volume, arterial CO_2 tension and respiratory activity. J. appl. Physiol. 20:647.

ZACKON, H., DESPAS, P.J. and ANTHONISEN, N.R. (1976) Occlusion pressure responses in asthma and chronic destructive pulmonary disease. Am. Rev. Resp. Dis. 114:917.

ZECHMAN, F., HALL, F.G. and HULL, W.E. (1957) Effect of graded resistance to tracheal airflow in man. J. appl. Physiol. 10:357.

* DAVIDSON, J.T., WASSERMAN, K., LILLINGTON, G.A. and SCHMIDT, R.W. (1966) Pulmonary function testing in the rabbit. J.Appl.Physiol. 21:1094

CAMPBELL, E.J.M. and HOWELL, J.B.L. (1962) Rebreathing method for measurement of mixed venous PCO_2. B.Med. J. 2:630

Appendix 1. Astrand's table for prediction of maximal oxygen uptake from heart rate and work load on a bicycle ergometer.

Heart rate	Maxial Oxygen Uptake litres/min.					Heart rate	Maxial Oxygen Uptake litres/min.				
	300 kpm/ min	600 kpm/ min	900 kpm/ min	1200 kpm/ min	1500 kpm/ min		300 kpm/ min	600 kpm/ min	900 kpm/ min	1200 kpm/ min	1500 kpm/ min
120	2.2	3.5	4.8			148		2.4	3.2	4.3	5.4
121	2.2	3.4	4.7			149		2.3	3.2	4.3	5.4
122	2.2	3.4	4.6			150		2.3	3.2	4.2	5.3
123	2.1	3.4	4.6			151		2.3	3.1	4.2	5.2
124	2.1	3.3	4.5	6.0		152		2.3	3.1	4.1	5.2
125	2.0	3.2	4.4	5.9		153		2.2	3.0	4.1	5.1
126	2.0	3.2	4.4	5.8		154		2.2	3.0	4.0	5.1
127	2.0	3.1	4.3	5.7		155		2.2	3.0	4.0	5.0
128	2.0	3.1	4.2	5.6		156		2.2	2.9	4.0	5.0
129	1.9	3.0	4.2	5.6		157		2.1	2.9	3.9	4.9
130	1.9	3.0	4.1	5.5		158		2.1	2.9	3.9	4.9
131	1.9	2.9	4.0	5.4		159		2.1	2.8	3.8	4.8
132	1.8	2.9	4.0	5.3		160		2.1	2.8	3.8	4.8
133	1.8	2.8	3.9	5.3		161		2.0	2.8	3.7	4.7
134	1.8	2.8	3.9	5.2		162		2.0	2.8	3.7	4.6
135	1.7	2.8	3.8	5.1		163		2.0	2.8	3.7	4.6
136	1.7	2.7	3.8	5.0		164		2.0	2.7	3.6	4.5
137	1.7	2.7	3.7	5.0		165		2.0	2.7	3.6	4.5
138	1.6	2.7	3.7	4.9		166		1.9	2.7	3.6	4.5
139	1.6	2.6	3.6	4.8		167		1.9	2.6	3.5	4.4
140	1.6	2.6	3.6	4.8	6.0	168		1.9	2.6	3.5	4.4
141		2.6	3.5	4.7	5.9	169		1.9	2.6	3.5	4.3
142		2.5	3.5	4.6	5.8	170		1.8	2.6	3.4	4.3
143		2.5	3.4	4.6	5.7						
144		2.5	3.4	4.5	5.7						
145		2.4	3.4	4.5	5.6						
146		2.4	3.3	4.4	5.6						
147		2.4	3.3	4.4	5.5						

Heart rate	Maxial Oxygen Uptake litres/min.					Heart rate	Maxial Oxygen Uptake litres/min.				
	300 kpm/ min	450 kpm/ min	600 kpm/ min	750 kpm/ min	900 kpm/ min		300 kpm/ min	450 kpm/ min	600 kpm/ min	750 kpm/ min	900 kpm/ min
120	2.6	3.4	4.1	4.8		148	1.6	2.1	2.6	3.1	3.6
121	2.5	3.3	4.0	4.8		149		2.1	2.6	3.0	3.5
122	2.5	3.2	3.9	4.7		150		2.0	2.5	3.0	3.5
123	2.4	3.1	3.9	4.6		151		2.0	2.5	3.0	3.4
124	2.4	3.1	3.8	4.5		152		2.0	2.5	2.9	3.4
125	2.3	3.0	3.7	4.4		153		2.0	2.4	2.9	3.3
126	2.3	3.0	3.6	4.3		154		2.0	2.4	2.8	3.3
127	2.2	2.9	3.5	4.2		155		1.9	2.4	2.8	3.2
128	2.2	2.8	3.5	4.2	4.8	156		1.9	2.3	2.8	3.2
129	2.2	2.8	3.4	4.1	4.8	157		1.9	2.3	2.7	3.2
130	2.1	2.7	3.4	4.0	4.7	158		1.8	2.3	2.7	3.1
131	2.1	2.7	3.4	4.0	4.6	159		1.8	2.2	2.7	3.1
132	2.0	2.7	3.3	3.9	4.5	160		1.8	2.2	2.6	3.0
133	2.0	2.6	3.2	3.8	4.4	161		1.8	2.2	2.6	3.0
134	2.0	2.6	3.2	3.8	4.4	162		1.8	2.2	2.6	3.0
135	2.0	2.6	3.1	3.7	4.3	163		1.7	2.2	2.6	2.9
136	1.9	2.5	3.1	3.6	4.2	164		1.7	2.1	2.5	2.9
137	1.9	2.5	3.0	3.6	4.2	165		1.7	2.1	2.5	2.9
138	1.8	2.4	3.0	3.5	4.1	166		1.7	2.1	2.5	2.8
139	1.8	2.4	2.9	3.5	4.0	167		1.6	2.1	2.4	2.8
140	1.8	2.4	2.8	3.4	4.0	168		1.6	2.0	2.4	2.8
141	1.8	2.3	2.8	3.4	3.9	169		1.6	2.0	2.4	2.8
142	1.7	2.3	2.8	3.3	3.9	170		1.6	2.0	2.4	2.7
143	1.7	2.2	2.7	3.3	3.8						
144	1.7	2.2	2.7	3.2	3.8						
145	1.6	2.2	2.7	3.2	3.7						
146	1.6	2.2	2.6	3.2	3.7						
147	1.6	2.1	2.6	3.1	3.6						

APPENDIX 2.

Calculation of Maximum Oxygen Uptake - ml/kg×min.

Body Weight		Maximum Oxygen Uptake - litres/min.																							
pound	kg	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	3.0	3.1	3.2	3.3	3.4	3.5	3.6	3.7	3.8	3.9
110	50	30	32	34	36	38	40	42	44	46	48	50	52	54	56	58	60	62	64	66	68	70	72	74	76	78
112	51	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57	59	61	63	65	67	69	71	73	75	76
115	52	29	31	33	35	37	38	40	42	44	46	48	50	52	54	56	58	60	62	63	65	67	69	71	73	75
117	53	28	30	32	34	36	38	40	42	43	45	47	49	51	53	55	57	58	60	62	64	66	68	70	72	74
119	54	28	30	31	33	35	37	39	41	43	44	46	48	50	52	54	56	57	59	61	63	65	67	69	70	72
121	55	27	29	31	33	35	36	38	40	42	44	45	47	49	51	53	55	56	58	60	62	64	65	67	69	71
123	56	27	29	30	32	34	36	38	39	41	43	45	46	48	50	52	54	55	57	59	61	63	64	66	68	70
126	57	26	28	30	32	33	35	37	39	40	42	44	46	47	49	51	53	54	56	58	60	61	63	65	67	68
128	58	26	28	29	31	33	34	36	38	40	41	43	45	47	48	50	52	53	55	57	59	60	62	64	66	67
130	59	25	27	29	31	32	34	36	37	39	41	42	44	46	47	49	51	53	54	56	58	59	61	63	64	66
132	60	25	27	28	30	32	33	35	37	38	40	42	43	45	47	48	50	52	53	55	57	58	60	62	63	65
134	61	25	26	28	30	31	33	34	36	38	39	41	43	44	46	48	49	51	52	54	56	57	59	61	62	64
137	62	24	26	27	29	31	32	34	35	37	39	40	42	44	45	47	48	50	52	53	55	56	58	60	61	63
139	63	24	25	27	29	30	32	33	35	37	38	40	41	43	44	46	48	49	51	52	54	56	57	59	60	62
141	64	23	25	27	28	30	31	33	34	36	38	39	41	42	44	45	47	48	50	52	53	55	56	58	59	61
143	65	23	25	26	28	29	31	32	34	35	37	38	40	42	43	45	46	48	49	51	52	54	55	57	58	60
146	66	23	24	26	27	29	30	32	33	35	36	38	39	41	42	44	45	47	48	50	52	53	55	56	58	59
148	67	22	24	25	27	28	30	31	33	34	36	37	39	40	42	43	45	46	48	49	51	52	54	55	57	58
150	68	22	24	25	26	28	29	31	32	34	35	37	38	40	41	43	44	46	47	49	50	51	53	54	56	57
152	69	22	23	25	26	28	29	30	32	33	35	36	38	39	41	42	43	45	46	48	49	51	52	54	55	57
154	70	21	23	24	26	27	29	30	31	33	34	36	37	39	40	41	43	44	46	47	49	50	51	53	54	56
157	71	21	23	24	25	27	28	30	31	32	34	35	37	38	39	41	42	44	45	46	48	49	51	52	54	55
159	72	21	22	24	25	26	28	29	31	32	33	35	36	38	39	40	42	43	44	46	47	49	50	51	53	54
161	73	21	22	23	25	26	27	29	30	32	33	34	36	37	38	40	41	42	44	45	47	48	49	51	52	53
163	74	20	22	23	24	26	27	28	30	31	32	34	35	36	38	39	41	42	43	45	46	47	49	50	51	53
165	75	20	21	23	24	25	27	28	29	31	32	33	35	36	37	39	40	41	43	44	45	47	48	49	51	52
168	76	20	21	22	24	25	26	28	29	30	32	33	34	36	37	38	39	41	42	43	45	46	47	49	50	51
170	77	19	21	22	23	25	26	27	29	30	31	32	34	35	36	38	39	40	42	43	44	45	47	48	49	51
172	78	19	21	22	23	24	26	27	28	29	31	32	33	35	36	37	38	40	41	42	44	45	46	47	49	50
174	79	19	20	22	23	24	25	27	28	29	30	32	33	34	35	37	38	39	41	42	43	44	46	47	48	49
176	80	19	20	21	23	24	25	26	28	29	30	31	33	34	35	36	38	39	40	41	43	44	45	46	48	49
179	81	19	20	21	22	23	25	26	27	28	30	31	32	33	35	36	37	38	40	41	42	43	44	46	47	48
181	82	18	20	21	22	23	24	26	27	28	29	30	32	33	34	35	37	38	39	40	41	43	44	45	46	48
183	83	18	19	20	22	23	24	25	27	28	29	30	31	33	34	35	36	37	39	40	41	42	43	45	46	47
185	84	18	19	20	21	23	24	25	26	27	29	30	31	32	33	35	36	37	38	39	40	42	43	44	45	46
187	85	18	19	20	21	22	24	25	26	27	28	29	31	32	33	34	35	36	38	39	40	41	42	44	45	46
190	86	17	19	20	21	22	23	24	26	27	28	29	30	31	33	34	35	36	37	38	40	41	42	43	44	45
192	87	17	18	20	21	22	23	24	25	26	28	29	30	31	32	33	34	36	37	38	39	40	41	43	44	45
194	88	17	18	19	20	22	23	24	25	26	27	28	30	31	32	33	34	35	36	38	39	40	41	42	43	44
196	89	17	18	19	20	21	22	24	25	26	27	28	29	30	31	33	34	35	36	37	38	39	40	42	43	44
198	90	17	18	19	20	21	22	23	24	26	27	28	29	30	31	32	33	34	36	37	38	39	40	41	42	43
201	91	16	18	19	20	21	22	23	24	25	26	27	29	30	31	32	33	34	35	36	37	38	40	41	42	43
203	92	16	17	18	20	21	22	23	24	25	26	27	28	29	30	32	33	34	35	36	37	38	39	40	41	42
205	93	16	17	18	19	20	22	23	24	25	26	27	28	29	30	31	32	33	34	35	37	38	39	40	41	42
207	94	16	17	18	19	20	21	22	23	24	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41
209	95	16	17	18	19	20	21	22	23	24	25	26	27	28	29	31	32	33	34	35	36	37	38	39	40	41
212	96	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	38	39	40	41
214	97	15	16	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
216	98	15	16	17	18	19	20	21	22	23	24	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
218	99	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
220	100	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39

APPENDIX 2 (contd.)

Calculation of Maximum Oxygen Uptake - ml/kg×min.

Body Weight		Maximum Oxygen Uptake - litres/min.																				
pound	kg	4.0	4.1	4.2	4.3	4.4	4.5	4.6	4.7	4.8	4.9	5.0	5.1	5.2	5.3	5.4	5.5	5.6	5.7	5.8	5.9	6.0
110	50	80	82	84	86	88	90	92	94	96	98	100	102	104	106	108	110	112	114	116	118	120
112	51	78	80	82	84	86	88	90	92	94	96	98	100	102	104	106	108	110	112	114	116	118
115	52	77	79	81	83	85	87	89	90	92	94	96	98	100	102	104	106	108	110	112	113	115
117	53	75	77	79	81	83	85	87	89	91	92	94	96	98	100	102	104	106	108	109	111	113
119	54	74	76	78	80	81	83	85	87	89	91	93	94	96	98	100	102	104	106	107	109	111
121	55	73	75	76	78	80	82	84	85	87	89	91	93	95	96	98	100	102	104	105	107	109
123	56	71	73	75	77	79	80	82	84	86	88	89	91	93	95	96	98	100	102	104	105	107
126	57	70	72	74	75	77	79	81	82	84	86	88	89	91	93	95	96	98	100	102	104	105
128	58	69	71	72	74	76	78	79	81	83	84	86	88	90	91	93	95	97	98	100	102	103
130	59	68	69	71	73	75	76	78	80	81	83	85	86	88	90	92	93	95	97	98	100	102
132	60	67	68	70	72	73	75	77	78	80	82	83	85	87	88	90	92	93	95	97	98	100
134	61	66	67	69	70	72	74	75	77	79	80	82	84	85	87	89	90	92	93	95	97	98
137	62	65	66	68	69	71	73	74	76	77	79	81	82	84	85	87	89	90	92	94	95	97
139	63	63	65	67	68	70	71	73	75	76	78	79	81	83	84	86	87	89	90	92	94	95
141	64	63	64	66	67	69	70	72	73	75	77	78	80	81	83	84	86	88	89	91	92	94
143	65	62	63	65	66	68	69	71	72	74	75	77	78	80	82	83	85	86	88	89	91	92
146	66	61	62	64	65	67	68	70	71	73	74	76	77	79	80	82	83	85	86	88	89	91
148	67	60	61	63	64	66	67	69	70	72	73	75	76	78	79	81	82	84	85	87	88	90
150	68	59	60	62	63	65	66	68	69	71	72	74	75	76	78	79	81	82	84	85	87	88
152	69	58	59	61	62	64	65	67	68	70	71	72	74	75	77	78	80	81	83	84	86	87
154	70	57	59	60	61	63	64	66	67	69	70	71	73	74	76	77	79	80	81	83	84	86
157	71	56	58	59	61	62	63	65	66	68	69	70	72	73	75	76	77	79	80	82	83	85
159	72	56	57	58	60	61	63	64	65	67	68	69	71	72	74	75	76	78	79	81	82	83
161	73	55	56	58	59	60	62	63	64	66	67	68	70	71	73	74	75	77	78	79	81	82
163	74	54	55	57	58	59	61	62	64	65	66	68	69	70	72	73	74	76	77	78	80	81
165	75	53	55	56	57	59	60	61	63	64	65	67	68	69	71	72	73	75	76	77	79	80
168	76	53	54	55	57	58	59	61	62	63	64	66	67	68	70	71	72	74	75	76	78	79
170	77	52	53	55	56	57	58	60	61	62	64	65	66	68	69	70	71	73	74	75	77	78
172	78	51	53	54	55	56	58	59	60	62	63	64	65	67	68	69	71	72	73	74	76	77
174	79	51	52	53	54	56	57	58	59	61	62	63	65	66	67	68	70	71	72	73	75	76
176	80	50	51	53	54	55	56	58	59	60	61	63	64	65	66	68	69	70	71	72	74	75
179	81	49	51	52	53	54	56	57	58	59	60	62	63	64	65	67	68	69	70	72	73	74
181	82	49	50	51	52	54	55	56	57	59	60	61	62	63	65	66	67	68	70	71	72	73
183	83	48	49	51	52	53	54	55	57	58	59	60	61	63	64	65	66	67	69	70	71	72
185	84	48	49	50	51	52	54	55	56	57	58	60	61	62	63	64	65	67	68	69	70	71
187	85	47	48	49	51	52	53	54	55	56	58	59	60	61	62	64	65	66	67	68	69	71
190	86	47	48	49	50	51	52	53	55	56	57	58	59	60	62	63	64	65	66	67	69	70
192	87	46	47	48	49	51	52	53	54	55	56	57	59	60	61	62	63	64	66	67	68	69
194	88	45	47	48	49	50	51	52	53	55	56	57	58	59	60	61	63	64	65	66	67	68
196	89	45	46	47	48	49	51	52	53	54	55	56	57	58	60	61	62	63	64	65	66	67
198	90	44	46	47	48	49	50	51	52	53	54	56	57	58	59	60	61	62	63	64	66	67
201	91	44	45	46	47	48	49	51	52	53	54	55	56	57	58	59	60	62	63	64	65	66
203	92	43	45	46	47	48	49	50	51	52	53	54	55	57	58	59	60	61	62	63	64	65
205	93	43	44	45	46	47	48	49	51	52	53	54	55	56	57	58	59	60	61	62	63	65
207	94	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	59	60	61	62	63	64
209	95	42	43	44	45	46	47	48	49	51	52	53	54	55	56	57	58	59	60	61	62	63
212	96	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	63
214	97	41	42	43	44	45	46	47	48	49	51	52	53	54	55	56	57	58	59	60	61	62
216	98	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61
218	99	40	41	42	43	44	45	46	47	48	49	51	52	53	54	55	56	57	58	59	60	61
220	100	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60